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(57) Abstract

The invention provides human phosphorylation effectors (PHSP) and polynucleotides which identify and encode PHSP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of PHSP.

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PHOSPHORYLATION EFFECTORS

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of phosphorylation effectors and to the use of these sequences in the diagnosis, treatment, and prevention of cell proliferative, immune, and neuronal disorders.

Kinases and phosphatases are critical components of intracellular signal transduction mechanisms. Kinases catalyze the transfer of high energy phosphate groups from adenosine triphosphate (ATP) to various target proteins. Phosphatases, in contrast, remove phosphate groups from proteins. Reversible protein phosphorylation is the main strategy for regulating protein activity in eukaryotic cells. In general, proteins are activated by phosphorylation in response to extracellular signals such as hormones, neurotransmitters, and growth and differentiation factors. Protein dephosphorylation occurs when down-regulation of a signaling pathway is required. The coordinate activities of kinases and phosphatases regulate key cellular processes such as proliferation, differentiation, and cell cycle progression. Kinases comprise the largest known enzyme superfamily and are widely varied in their substrate specificities. Kinases may be categorized based on the specific amino acid residues that are phosphorylated in their substrates: protein tyrosine kinases (PTK) phosphorylate tyrosine residues, and protein serine/threonine kinases (STK) phosphorylate serine and/or threonine residues. Almost all kinases contain a conserved 250-300 amino acid catalytic domain. This domain can be further divided into 11 subdomains. N-terminal subdomains I-IV fold into a two-lobed structure which binds and orients the ATP donor molecule, and subdomain V spans the two lobes. C-terminal subdomains VIA-XI bind the protein substrate and transfer the gamma phosphate from ATP to the hydroxyl group of a serine, threonine, or tyrosine residue. Each of the 11 subdomains contains specific catalytic residues or amino acid motifs characteristic of that subdomain. For example, subdomain I contains an 8-amino acid glycine-rich ATP binding consensus motif, subdomain II contains a critical lysine residue required for maximal catalytic activity, and subdomains VI and IX comprise the highly conserved catalytic core. Kinases may also be categorized by additional amino acid sequences, generally between 5 and 100 residues, which either flank or occur within the kinase domain. These additional amino acid sequences regulate kinase activity and determine substrate specificity. (Reviewed in Hardie, G. and Hanks, S. (1995) The Protein Kinase Facts Books, Vol I:7-20 Academic Press, San Diego, CA.)

STKs include both protein kinase A (PKA) and calcium-dependent protein kinase C

(PKC), both of which transduce signals from plasma membrane receptors. The activities of PKA and PKC are directly regulated by second messenger signaling molecules such as cyclic AMP and diacylglycerol, respectively. A novel kinase identified by genetic analysis in the fission yeast Schizosaccharomyces pombe is encoded by the *cek1*$^+$ gene and is related to both PKA and PKC (Samejima, I. and Yanagida, M. (1994) Mol. Cell. Biol. 14:6361-6371). *cek1*$^+$ encodes an unusually large kinase of 1309 amino acids. The kinase domain spans residues 585 to 987, and 112 additional amino acids are present in this domain between subdomains VII and VIII. Overexpression of *cek1*$^+$ suppresses mutations in *cut8*$^+$, a gene required for chromosome segregation during mitosis. Therefore, *cek1*$^+$ may encode a unique member of the PKA/PKC protein family with a role in mitotic signaling and cell cycle progression.

PTKs may be classified as either transmembrane or nontransmembrane proteins. Transmembrane tyrosine kinases function as receptors for most growth factors. Binding of growth factor to the receptor activates the transfer of a phosphate group from ATP to selected tyrosine side chains of the receptor itself and other specific second messenger proteins. Growth factors (GF) that associate with receptor PTKs include epidermal GF, platelet-derived GF, fibroblast GF, hepatocyte GF, insulin and insulin-like GFs, nerve GF, vascular endothelial GF, and macrophage colony stimulating factor. Nontransmembrane PTKs form signaling complexes with the cytosolic domains of plasma membrane receptors. Receptors that signal through nontransmembrane PTKs include cytokine, hormone, and antigen-specific lymphocytic receptors. Many PTKs were first identified as oncogene products in cancer cells in which PTK activation was no longer subject to normal cellular controls. In fact, about one third of the known oncogenes encode PTKs. Furthermore, cellular transformation (oncogenesis) is often accompanied by increased tyrosine phosphorylation activity (Charbonneau, H. and Tonks, N. K. (1992) Annu. Rev. Cell Biol. 8:463-93). Regulation of PTK activity may therefore be an important strategy in controlling some types of cancer.

Some kinases utilize carbohydrates as their substrates and are important for glucose metabolism. For example, glycolysis employs four distinct kinases to effect the conversion of glucose to pyruvate, a key metabolite in the production of ATP. One of these enzymes is phosphofructokinase (PFK) which catalyzes the transfer of phosphate from ATP to fructose 6-phosphate. PFK is an allosteric enzyme and a key regulator of glycolysis. In certain genetic muscle disorders, such as muscle phosphofructokinase deficiency type VII, phosphofructokinase activity is absent in muscle and deficient in red blood cells. As a result, afflicted individuals suffer from mild hemolytic anemia and muscle pain (Isselbacher, K.J. et al. (1994) Harrison's Principles of Internal Medicine, McGraw-Hill, New York, NY, p. 2102).

Kinase-mediated phosphorylation is antagonized by the activity of phosphatases, which

remove phosphate groups by hydrolysis. Phosphatases are classified into one of three evolutionarily distinct families: the protein serine/threonine phosphatases (PPs), the protein tyrosine phosphatases, and the acid/alkaline phosphatases. PPs may be further categorized into four distinct groups: PP-I, PP-IIA, PP-IIB, and PP-IIC. (Cohen, P. (1989) Annu. Rev. Biochem. 58:453-508). PP-I, in particular, dephosphorylates many of the proteins phosphorylated by PKA and is therefore an important regulator of signal transduction pathways. Kinase-activated proteins which bind to and inhibit PP-I have been identified. These inhibitors potentiate the activity of kinases such as PKA by allowing protein substrates to remain in their phosphorylated, activated state. A novel inhibitor of PP-1 has been purified from porcine aorta (Eto, M. et al. (1995) J. Biochem. 118:1104-1107; Eto, M. et al. (1997) FEBS Lett. 410:356-360). This inhibitor, called CPI17, is 147 amino acids in length and is activated by PKC. CPI17 expression is restricted to smooth muscle tissues such as aorta and bladder, suggesting that CPI17 functions in PKC-mediated signal transduction pathways in these tissues, possibly through a calcium-dependent mechanism.

The discovery of new phosphorylation effectors and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative, immune, and neuronal disorders.

SUMMARY OF THE INVENTION

The invention features substantially purified polypeptides, phosphorylation effectors, referred to collectively as "PHSP" and individually as "PHSP-1 to PHSP-31",. In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID NO:1-31, and fragments thereof. The invention also provides an isolated and purified polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof. The invention also includes an isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments

thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

The invention also provides a method for detecting a polynucleotide in a sample containing nucleic acids, the method comprising the steps of (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:32-62, and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:32-62, and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:32-62, and fragments thereof.

The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof. In another aspect, the expression vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing at least a fragment of a polynucleotide under conditions suitable for the expression of the polypeptide; and (b) recovering the polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected from the group consisting of SEQ ID NO:1-31, and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of PHSP, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group

consisting of SEQ ID NO:1-31, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of PHSP, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows nucleotide and polypeptide sequence identification numbers (SEQ ID NO), clone identification numbers (clone ID), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding PHSP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods and algorithms used for identification of PHSP.

Table 3 shows the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis, diseases, disorders, or conditions associated with these tissues, and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding PHSP were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze PHSP, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described

herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"PHSP" refers to the amino acid sequences of substantially purified PHSP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and preferably the human species, from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which, when bound to PHSP, increases or prolongs the duration of the effect of PHSP. Agonists may include proteins, nucleic acids, carbohydrates, or any other molecules which bind to and modulate the effect of PHSP.

An "allelic variant" is an alternative form of the gene encoding PHSP. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. Any given natural or recombinant gene may have none, one, or many allelic forms. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding PHSP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polynucleotide the same as PHSP or a polypeptide with at least one functional characteristic of PHSP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding PHSP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding PHSP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent PHSP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of PHSP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, positively charged amino acids may include lysine and arginine, and amino acids with uncharged polar head groups having similar hydrophilicity values may include leucine, isoleucine,

and valine; glycine and alanine; asparagine and glutamine; serine and threonine; and phenylalanine and tyrosine.

The terms "amino acid" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. In this context, "fragments," "immunogenic fragments," or "antigenic fragments" refer to fragments of PHSP which are preferably at least 5 to about 15 amino acids in length, most preferably at least 14 amino acids, and which retain some biological activity or immunological activity of PHSP. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which, when bound to PHSP, decreases the amount or the duration of the effect of the biological or immunological activity of PHSP. Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules which decrease the effect of PHSP.

The term "antibody" refers to intact molecules as well as to fragments thereof, such as Fab, $F(ab')_2$, and Fv fragments, which are capable of binding the epitopic determinant. Antibodies that bind PHSP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that fragment of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (given regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell,

the complementary nucleotides combine with natural sequences produced by the cell to form duplexes and to block either transcription or translation. The designation "negative" can refer to the antisense strand, and the designation "positive" can refer to the sense strand.

The term "biologically active," refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic PHSP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" or "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acids strands, and in the design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" or a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding PHSP or fragments of PHSP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence"refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of more than one Incyte Clone using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

The term "correlates with expression of a polynucleotide" indicates that the detection of the presence of nucleic acids, the same or related to a nucleic acid sequence encoding PHSP, by northern analysis is indicative of the presence of nucleic acids encoding PHSP in a sample, and

thereby correlates with expression of the transcript from the polynucleotide encoding PHSP.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" and "% identity" refer to the percentage of sequence similarity found in a comparison of two or more amino acid or nucleic acid sequences. Percent identity can be determined electronically, e.g., by using the MEGALIGN program (DNASTAR, Madison WI) which creates alignments between two or more sequences according to methods selected by the user, e.g., the clustal method. (See, e.g., Higgins, D.G. and P.M. Sharp (1988) Gene 73:237-244.) The clustal algorithm groups sequences into clusters by examining the distances between all pairs. The clusters are aligned pairwise and then in groups. The percentage similarity between two amino acid sequences, e.g., sequence A and sequence B, is calculated by dividing the length of sequence A, minus the number of gap residues in sequence A, minus the number of gap residues in sequence B, into the sum of the residue matches between sequence A

and sequence B, times one hundred. Gaps of low or of no similarity between the two amino acid sequences are not included in determining percentage similarity. Percent identity between nucleic acid sequences can also be counted or calculated by other methods known in the art, e.g., the Jotun Hein method. (See, e.g., Hein, J. (1990) Methods Enzymol. 183:626-645.) Identity between sequences can also be determined by other methods known in the art, e.g., by varying hybridization conditions.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" or "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively, to the sequence found in the naturally occurring molecule.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" or "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

The term "modulate" refers to a change in the activity of PHSP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of PHSP.

The phrases "nucleic acid" or "nucleic acid sequence," as used herein, refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to

DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material. In this context, "fragments" refers to those nucleic acid sequences which, comprise a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:32-62, for example, as distinct from any other sequence in the same genome. For example, a fragment of SEQ ID NO:32-62 is useful in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:32-62 from related polynucleotide sequences. A fragment of SEQ ID NO:32-62 is at least about 15-20 nucleotides in length. The precise length of the fragment of SEQ ID NO:32-62 and the region of SEQ ID NO:32-62 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment. In some cases, a fragment, when translated, would produce polypeptides retaining some functional characteristic, e.g., antigenicity, or structural domain characteristic, e.g., ATP-binding site, of the full-length polypeptide

The terms "operably associated" or "operably linked" refer to functionally related nucleic acid sequences. A promoter is operably associated or operably linked with a coding sequence if the promoter controls the translation of the encoded polypeptide. While operably associated or operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements, e.g., repressor genes, are not contiguously linked to the sequence encoding the polypeptide but still bind to operator sequences that control expression of the polypeptide.

The term "oligonucleotide" refers to a nucleic acid sequence of at least about 6 nucleotides to 60 nucleotides, preferably about 15 to 30 nucleotides, and most preferably about 20 to 25 nucleotides, which can be used in PCR amplification or in a hybridization assay or microarray. "Oligonucleotide" is substantially equivalent to the terms "amplimer," "primer," "oligomer," and "probe," as these terms are commonly defined in the art.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding PHSP, or fragments thereof, or PHSP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" or "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, or an antagonist. The interaction is dependent upon

the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

"Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "variant" of PHSP polypeptides refers to an amino acid sequence that is altered by one or more amino acid residues. The variant may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties (e.g., replacement of leucine with isoleucine). More rarely, a variant may have "nonconservative" changes (e.g., replacement of

glycine with tryptophan). Analogous minor variations may also include amino acid deletions or insertions, or both. Guidance in determining which amino acid residues may be substituted, inserted, or deleted without abolishing biological or immunological activity may be found using computer programs well known in the art, for example, LASERGENE software (DNASTAR).

The term "variant," when used in the context of a polynucleotide sequence, may encompass a polynucleotide sequence related to PHSP. This definition may also include, for example, "allelic" (as defined above), "splice," "species," or "polymorphic" variants. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or an absence of domains. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

THE INVENTION

The invention is based on the discovery of new human phosphorylation effectors (PHSP), the polynucleotides encoding PHSP, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative, immune, and neuronal disorders.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding PHSP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each PHSP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The clones in column 5 were used to assemble the consensus nucleotide sequence of each PHSP and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO and column 2 shows the number of amino acid residues in each polypeptide. Columns 3 and 4 show potential phosphorylation sites and potential glycosylation sites, respectively. Column 5 shows the amino acid residues comprising signature sequences and motifs. Column 6 shows homologous sequences as identified by BLAST analysis, while column 7 shows analytical methods used to identify each polypeptide through sequence

homology and protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding PHSP. The first column of Table 3 lists the SEQ ID NOs. Column 2 lists tissue categories which express PHSP as a fraction of total tissue categories expressing PHSP. Column 3 lists diseases, disorders, or conditions associated with those tissues expressing PHSP. Column 4 lists the vectors used to subclone the cDNA library.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding PHSP were isolated. Column 1 references the SEQ ID NO, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

The following fragments of the nucleotide sequences encoding PHSP are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:32-62 and to distinguish between SEQ ID NO:32-62 and related polynucleotide sequences. The useful fragments include, the fragment of SEQ ID NO:32 from about nucleotide 81 to about nucleotide 110; the fragment of SEQ ID NO:33 from about nucleotide 323 to about nucleotide 352; the fragment of SEQ ID NO:34 from about nucleotide 83 to about nucleotide 112; the fragment of SEQ ID NO:35 from about nucleotide 524 to about nucleotide 553; the fragment of SEQ ID NO:36 from about nucleotide 275 to about nucleotide 346; the fragment of SEQ ID NO:37 from about nucleotide 1328 to about nucleotide 1396; the fragment of SEQ ID NO:38 from about nucleotide 245 to about nucleotide 304; the fragment of SEQ ID NO:39 from about nucleotide 1253 to about nucleotide 1312; the fragment of SEQ ID NO:41 from about nucleotide 117 to about nucleotide 170; the fragments of SEQ ID NO:42 from about nucleotide 109 to about nucleotide 153, and from about nucleotide 325 to about nucleotide 369; the fragments of SEQ ID NO:43 from about nucleotide 380 to about nucleotide 424, and from about nucleotide 1190 to about nucleotide 1234; the fragment of SEQ ID NO:44 from about nucleotide 1 to about nucleotide 46; the fragment of SEQ ID NO:45 from about nucleotide 533 to about nucleotide 577; the fragments of SEQ ID NO:46 from about nucleotide 109 to about nucleotide 153, and from about nucleotide 379 to about nucleotide 423; the fragment of SEQ ID NO:47 from about nucleotide 1730 to about nucleotide 1774; the fragment of SEQ ID NO:48 from about nucleotide 433 to about nucleotide 477; the fragment of SEQ ID NO:49 from about nucleotide 1117 to about nucleotide 1155; the fragment of SEQ ID NO:50 from about nucleotide 166 to about nucleotide 213; the fragment of SEQ ID NO:51 from about nucleotide 60 to about nucleotide 95; the fragment of SEQ ID NO:52 from about nucleotide 326 to about nucleotide 370; the fragment of SEQ ID NO:53 from about nucleotide 25 to about nucleotide 66; the fragment of SEQ ID NO:54 from about nucleotide 55 to

about nucleotide 102; the fragment of SEQ ID NO:55 from about nucleotide 138 to about nucleotide 167; the fragment of SEQ ID NO:56 from about nucleotide 29 to about nucleotide 58; the fragment of SEQ ID NO:57 from about nucleotide 455 to about nucleotide 484; the fragment of SEQ ID NO:58 from about nucleotide 226 to about nucleotide 255; the fragment of SEQ ID NO:59 from about nucleotide 557 to about nucleotide 598; the fragment of SEQ ID NO:60 from about nucleotide 284 to about nucleotide 325; the fragment of SEQ ID NO:61 from about nucleotide 1043 to about nucleotide 1090; and the fragment of SEQ ID NO:62 from about nucleotide 84 to about nucleotide 132. The polypeptides encoded by the fragments of SEQ ID NO:32-62 are useful, for example, as immunogenic peptides.

The invention also encompasses PHSP variants. A preferred PHSP variant is one which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the PHSP amino acid sequence, and which contains at least one functional or structural characteristic of PHSP.

The invention also encompasses polynucleotides which encode PHSP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:32-62, which encodes PHSP.

The invention also encompasses a variant of a polynucleotide sequence encoding PHSP. In particular, such a variant polynucleotide sequence will have at least about 80%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding PHSP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:32-62 which has at least about 80%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:32-62. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of PHSP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding PHSP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring PHSP, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode PHSP and its variants are preferably capable of hybridizing to the nucleotide sequence of the naturally occurring PHSP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding

PHSP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding PHSP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode PHSP and PHSP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding PHSP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:32-62 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 % formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

The washing steps which follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can

be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include temperature of at least about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art.

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 (Hamilton, Reno NV), Peltier thermal cycler 200 (PTC200; MJ Research, Watertown MA) and the ABI CATALYST 800 (Perkin-Elmer). Sequencing is then carried out using the ABI 373 or 377 DNA sequencing systems (Perkin-Elmer), or the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding PHSP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions

and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-306). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 primer analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode PHSP may be cloned in recombinant DNA molecules that direct expression of PHSP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express PHSP.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter PHSP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction

sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding PHSP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucl. Acids Res. Symp. Ser. 215-223, and Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 225-232.) Alternatively, PHSP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of PHSP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g, Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

In order to express a biologically active PHSP, the nucleotide sequences encoding PHSP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding PHSP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding PHSP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding PHSP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding PHSP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory

Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding PHSP. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus,TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding PHSP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding PHSP can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or pSPORT1 plasmid (Life Technologies). Ligation of sequences encoding PHSP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of PHSP are needed, e.g. for the production of antibodies, vectors which direct high level expression of PHSP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of PHSP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Grant et al. (1987) Methods Enzymol. 153:516-54; and Scorer, C. A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of PHSP. Transcription of sequences encoding PHSP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY,

pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding PHSP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses PHSP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of PHSP in cell lines is preferred. For example, sequences encoding PHSP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk*⁻ or *apr*⁻ cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides, neomycin and G-418; and *als* or *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), ß glucuronidase and its substrate ß-glucuronide, or luciferase and its substrate luciferin may

be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding PHSP is inserted within a marker gene sequence, transformed cells containing sequences encoding PHSP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding PHSP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding PHSP and that express PHSP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of PHSP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on PHSP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St Paul MN, Sect. IV; Coligan, J. E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding PHSP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding PHSP, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for

ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding PHSP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode PHSP may be designed to contain signal sequences which direct secretion of PHSP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38), are available from the American Type Culture Collection (ATCC, Bethesda MD) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding PHSP may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric PHSP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of PHSP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the PHSP encoding sequence and the heterologous protein sequence, so that PHSP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled PHSP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract systems (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, preferably ^{35}S-methionine.

Fragments of PHSP may be produced not only by recombinant production, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Various fragments of PHSP may be synthesized separately and then combined to produce the full length molecule.

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of PHSP and protein phosphatases. In addition, the expression of PHSP is closely associated with reproductive tissue, nervous tissue, gastrointestinal tissue, cell proliferation, cancer, inflammation, and immune response. Therefore, PHSP appears to play a role in cell proliferative, immune, and neuronal disorders. In the treatment of disorders associated with increased PHSP expression or activity, it is desirable to decrease the expression or activity of PHSP. In the treatment of disorders associated with decreased PHSP expression or activity, it is desirable to increase the expression or activity of PHSP.

Therefore, in one embodiment, PHSP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PHSP. Examples of such disorders include, but are not limited to, a cell proliferative disorder, such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immune disorder, such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyenodocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis,

hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; and a neuronal disorder, such as akathesia, Alzheimer's disease, amnesia, amyotrophic lateral sclerosis, bipolar disorder, catatonia, dementia, depression, diabetic neuropathy, Down's syndrome, tardive dyskinesia, dystonias, epilepsy, Huntington's disease, peripheral neuropathy, multiple sclerosis, neurofibromatosis, Parkinson's disease, paranoid psychoses, postherpetic neuralgia, schizophrenia, and Tourette's disorder.

In another embodiment, a vector capable of expressing PHSP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PHSP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified PHSP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PHSP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of PHSP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PHSP including, but not limited to, those listed above.

In a further embodiment, an antagonist of PHSP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of PHSP. Examples of such disorders include, but are not limited to, those described above. In one aspect, an antibody which specifically binds PHSP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissue which express PHSP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding PHSP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of PHSP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of PHSP may be produced using methods which are generally known in the art. In particular, purified PHSP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind PHSP. Antibodies to PHSP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are especially preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with PHSP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to PHSP have an amino acid sequence consisting of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of PHSP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to PHSP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce PHSP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton

D.R. (1991) Proc. Natl. Acad. Sci. 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. 86: 3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for PHSP may also be generated. For example, such fragments include, but are not limited to, F(ab')2 fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between PHSP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering PHSP epitopes is preferred, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for PHSP. Affinity is expressed as an association constant, K_a, which is defined as the molar concentration of PHSP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple PHSP epitopes, represents the average affinity, or avidity, of the antibodies for PHSP. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular PHSP epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the PHSP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of PHSP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J. E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For

example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is preferred for use in procedures requiring precipitation of PHSP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding PHSP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding PHSP may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary to polynucleotides encoding PHSP. Thus, complementary molecules or fragments may be used to modulate PHSP activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding PHSP.

Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding PHSP. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

Genes encoding PHSP can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding PHSP. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding PHSP. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, are preferred. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA

by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding PHSP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding PHSP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nature Biotechnology 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such

therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of PHSP, antibodies to PHSP, and mimetics, agonists, antagonists, or inhibitors of PHSP. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acid. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of PHSP, such labeling would include amount, frequency, and method of administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example PHSP or fragments thereof, antibodies of PHSP, and agonists, antagonists or inhibitors of PHSP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind PHSP may be used for the diagnosis of disorders characterized by expression of PHSP, or in assays to monitor patients being treated with PHSP or agonists, antagonists, or inhibitors of PHSP. Antibodies useful for diagnostic

purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for PHSP include methods which utilize the antibody and a label to detect PHSP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring PHSP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of PHSP expression. Normal or standard values for PHSP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to PHSP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of PHSP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding PHSP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of PHSP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of PHSP, and to monitor regulation of PHSP levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding PHSP or closely related molecules may be used to identify nucleic acid sequences which encode PHSP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding PHSP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the PHSP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:32-62 or from genomic sequences including promoters, enhancers, and introns of the PHSP gene.

Means for producing specific hybridization probes for DNAs encoding PHSP include the cloning of polynucleotide sequences encoding PHSP or PHSP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes <u>in vitro</u> by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a

variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S, or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding PHSP may be used for the diagnosis of disorders associated with expression of PHSP. Examples of such disorders include, but are not limited to, a cell proliferative disorder, such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immune disorder, such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyenodocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; and a neuronal disorder, such as akathesia, Alzheimer's disease, amnesia, amyotrophic lateral sclerosis, bipolar disorder, catatonia, dementia, depression, diabetic neuropathy, Down's syndrome, tardive dyskinesia, dystonias, epilepsy, Huntington's disease, peripheral neuropathy, multiple sclerosis, neurofibromatosis, Parkinson's disease, paranoid psychoses, postherpetic neuralgia, schizophrenia, and Tourette's disorder. The polynucleotide sequences encoding PHSP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered PHSP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding PHSP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding PHSP may be labeled by standard methods and added to a fluid or tissue sample

from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantitated and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding PHSP in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of PHSP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding PHSP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding PHSP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding PHSP, or a fragment of a polynucleotide complementary to the polynucleotide encoding PHSP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantitation of closely related DNA or RNA sequences.

Methods which may also be used to quantify the expression of PHSP include radiolabeling

or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in an ELISA format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding PHSP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) site. Correlation between the location of the gene encoding PHSP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known.

New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, PHSP, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between PHSP and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with PHSP, or fragments thereof, and washed. Bound PHSP is then detected by methods well known in the art. Purified PHSP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding PHSP specifically compete with a test compound for binding PHSP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PHSP.

In additional embodiments, the nucleotide sequences which encode PHSP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 09/173,482, 09/123,494, 09/152,814, 09/229,005, 60/106,889, 60/109,093, and 60/113,796, are hereby expressly incorporated by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6). Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), pSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent E. coli cells including XL1-BLUE, XL1-BLUEMRF, or SOLR from Stratagene or DH5α, DH10B, or ELECTROMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids were recovered from host cells by in vivo excision, using the UNIZAP vector system (Stratagene) or cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid kit from QIAGEN.

Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a Fluoroskan II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Perkin-Elmer) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing systems (Perkin-Elmer) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR).

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST,

dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases, such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Str. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:32-62. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ database (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\%\ \text{sequence identity} \times \%\ \text{maximum BLAST score}}{100}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding PHSP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic,

developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation/trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

V. Extension of PHSP Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:32-62 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+}, $(NH_4)_2SO_4$, and β-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 μl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 μl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μl to 10 μl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulphoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:32-62 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:32-62 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μCi of [γ-^{32}P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba1, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon

membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under increasingly stringent conditions up to 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are compared.

VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, supra.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

VIII. Complementary Polynucleotides

Sequences complementary to the PHSP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring PHSP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of PHSP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the PHSP-encoding transcript.

IX. Expression of PHSP

Expression and purification of PHSP is achieved using bacterial or virus-based expression

systems. For expression of PHSP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express PHSP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of PHSP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding PHSP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E. K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, PHSP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from PHSP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch 10 and 16). Purified PHSP obtained by these methods can be used directly in the following activity assay.

X. Demonstration of PHSP Activity

PHSP protein kinase is measured by the phosphorylation of a substrate in the presence of gamma-labeled ^{32}P-ATP. PHSP is incubated with an appropriate substrate and ^{32}P-ATP in a buffered solution. ^{32}P-labeled product is separated from free ^{32}P-ATP by gel electrophoresis or chromatographic procedures, and the incorporated ^{32}P is quantified by phosphorimage analysis or using a scintillation counter. The amount of ^{32}P detected is proportional to the activity of PHSP in this assay. The specific amino acid residue phosphorylated by PHSP may be determined by

phosphoamino acid analysis of the labeled, hydrolyzed protein.

PHSP phosphatase activity is measured by the removal of phosphate from a [^{32}P]-labelled substrate. PHSP is incubated with an appropriate [^{32}P]-labelled substrate in a buffered solution. Reaction products are separated by gel electrophoresis or chromatographic procedures, and the level of ^{32}P associated with the substrate molecule is quantified by phospho-image analysis or scintillation counting. The difference in ^{32}P associated with untreated substrate versus PHSP-treated substrate is a measure of phosphatase activity and is proportional to PHSP activity.

XI. Functional Assays

PHSP function is assessed by expressing the sequences encoding PHSP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, preferably of endothelial or hematopoietic origin, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate properties, for example, their apoptotic state. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M. G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of PHSP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding PHSP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art.

Expression of mRNA encoding PHSP and other genes of interest can be analyzed by northern analysis or microarray techniques.

XII. Production of PHSP Specific Antibodies

PHSP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the PHSP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide activity by, for example, binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIII. Purification of Naturally Occurring PHSP Using Specific Antibodies

Naturally occurring or recombinant PHSP is substantially purified by immunoaffinity chromatography using antibodies specific for PHSP. An immunoaffinity column is constructed by covalently coupling anti-PHSP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing PHSP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PHSP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/PHSP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and PHSP is collected.

XIV. Identification of Molecules Which Interact with PHSP

PHSP, or biologically active fragments thereof, are labeled with ^{125}I Bolton-Hunter reagent. (See, e.g., Bolton et al. (1973) Biochem. J. 133:529.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled PHSP, washed, and any wells with labeled PHSP complex are assayed. Data obtained using different concentrations of PHSP are used to calculate values for the number, affinity, and association of PHSP with the candidate molecules.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

TABLE 1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	32	132240	BMARNOT02	132240H1 and 132240R1 (BMARNOT02), 3254142H1 (OVARTUN01), 1453821X14F1 and 1453821F6 (PENITUT01)
2	33	2180116	SININOT01	2180116H1 and 2180116T6 (SININOT01), 3046645H1 (HEAANOT01), 1918183H1 (PROSNOT06), and 1482405F1 (CORPNOT02)
3	34	2197671	SPLNFET02	2197671H1 (SPLNFET02), 666366X22R1 (SCORNOT01), 693783X14 (SYNORAT03), 824265X33F1 (PROSNOT06), 039482R1 and 039482F1 (HUVENOB01), 1453984T6 (PENITUT01), 1663987H1 (BRSTNOT09), and 125901R1 (LUNGNOT01)
4	35	2594943	OVARTUT02	2594943H1 (OVARTUT02), 3617557H1 (EPIPNOT01), 2269005R6 (UTRSNOT02), 1307764F6 (COLNFET02), 1377794F6 (LUNGNOT10), and 1286608H1 (BRAINOT11)
5	36	1513871	PANCTUT01	754239R6 (BRAITUT02), 1513871H1 (PANCTUT01), 2414420F6 (HNT3AZT01), 3291775F6 (BONRFET01), 3821451F6 (BONSTUT01)
6	37	156108	THP1PLB02	156108F1 and 156108H1 (THP1PLB02), 336346R6 (EOSIHET02), 1319528F1 (BLADNOT04), 2375549F6 (ISLTNOT01), SBFA04563F1, SBFA04977F1
7	38	2883243	UTRSTUT05	1342082F6 (COLNTUT03), 1933387T6 (COLNNOT16), 2766460F6 (BRSTNOT12), 2883243H1 (UTRSTUT05), 3524262H1 (ESOGTUN01), 3766487F6 (BRSTNOT24)

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
8	39	3173355	UTRSTUT04	1300803F6 and 1300803T6 (BRSTNOT07), 2477542F6 (SMCANOT01), 2477542T6 (SMCANOT01), 2875968H1 (THYRNOT10), 3173355F6 and 3173355H1 (UTRSTUT04), 3290825H1 (BONRFET01), 5192561H1 (OVARDIT06)
9	40	5116906	SMCBUNT01	267517F1 (HNT2NOT01), 263823R1 (HNT2AGT01), 5116906H1 (SMCBUNT01)
10	41	940589	ADRENOT03	029801R6 (SPLNFET01), 940589H1 (ADRENOT03), 1737403T6 (COLNNOT22), 1805477F6 and 1805477T6 (SINTNOT13), 2447613H1 (THP1NOT03), 3408563H1 (PROSTUS08), 3519506H1 (LUNGNON03), 3637343T6 (LUNGNOT30)
11	42	304421	TESTNOT04	304421H1, 304421X318B2, and 304421X323B2 (TESTNOT04), 2639579F6 (BONTNOT01), 2951859H1 (KIDNFET01)
12	43	1213802	BRSTTUT01	894574R1 (BRSTNOT05), 1213802H1 (BRSTTUT01), 1233414F1 and 1234238H1 (LUNGFET03), 1255782F2 and 1255782T1 (MENITUT03), 1455429F1 (COLNFET02), 1576102T1 (LNODNOT03), 2189267F6 (PROSNOT26), 2748179F6 (LUNGTUT11), 2831667H1 (TLYMNOT03), 3031229H1 (TLYMNOT05), 3054893H1 (LNODNOT08), 3797030F6 (SPLNNOT12), 3880154H1 (SPLNNOT11), 4852525H1 (TESTNOT10), 5514137H1 (BRADDIR01), 5518378H1 (LIVRDIR01)
13	44	1378134	LUNGNOT10	1378134H1 and 1378134X11 (LUNGNOT10), 2205185F6 (SPLNFET02), 4959694H1 (TLYMNOT05), SAMA00107F1, SAMA00160F1, SAMA00020F1

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
14	45	1490070	UCMCL5T01	432218H1 (BRAVUNT02), 1490070H1 (UCMCL5T01), 1535394F1 (SPLNNOT04), 1616509F6 and 1616509T6 (BRAITUT12), 2490845H1 (EOSITXT01), 2723789F6 (LUNGTUT10), SAOA00263F1
15	46	1997814	BRSTTUT03	855350R1 (NGANNOT01), 875417R1 (LUNGAST01), 895096R1 (BRSTNOT05), 1271348F1 (TESTTUT02), 1331289F6 (PANCNOT07), 1359243F1 (LUNGNOT12), 1540824T1 (SINTTUT01), 1839828H1 (EOSITXT01), 1997814H1 (BRSTTUT03), 2170638F6 (ENDCNOT03), 3751363F6 (UTRSNOT18)
16	47	2299715	BRSTNOT05	637354R6 and 637354T6 (NEUTGMT01), 1852144F6 (LUNGFET03), 2172576F6 (ENDCNOT03), 2232449F6 (PROSNOT16), 2299715H1 (BRSTNOT05), 2509737X325D2 (CONUTUT01), 2606210F6 (LUNGTUT07), 2692024F6 (LUNGNOT23), 2805893F6 (BLADTUT08), 2986160H1 (CARGDIT01), 3085382H1 (HEAONOT03), 3136101F6 and 3136587H1 (SMCCNOT01), 4249977H1 (BRADDIR01)
17	48	209854	SPLNNOT02	209854H1 and 209854T6 (SPLNNOT02), 3152165R6 and 3152165T6 (ADRENON04)
18	49	1384286	BRAITUT08	676123R6 and 676123T6 (CRBLNOT01), 989218X11 and 989218X12 (LVENNOT03), 1384286H1 (BRAITUT08), 3099868H1 (PROSBPT03), 4693167H1 (BRAENOT02)
19	50	1512656	PANCTUT01	322847X5 (EOSIHET02), 1253795T6 (LUNGFET03), 1512656H1 (PANCTUT01), 1561686X303D1 (SPLNNOT04), 2212305H1 (SINTFET03), 2697679H1 (UTRSNOT12), 3205172H1 (PENCNOT03), 5313318H1 (KIDETXS02)

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
20	51	2098635	BRAITUT02	1268848T1, 1268848X301F1, and 2157157H1 (BRAINOT09), 2098635H1 and 2098635R6 (BRAITUT02), 2198819F6, 2198819X301D4, 2198819X303D1, 2198819X309B2, and 2198819X309D4 (SPLNFET02), 2784975H2 (BRSTNOT13), 3320340H1 (PROSBPT03)
21	52	2446646	THP1NOT03	000297R6 and 000297X61 (U937NOT01), 2446646H1 (THP1NOT03), 2557274F6 (THYMNOT03)
22	53	2764911	BRSTNOT12	678618T6 and 678618X14 (UTRSNOT02), 2304126R6 (BRSTNOT05), 2764911H1 (BRSTNOT12), 2834475F6 (TLYMNOT03), 2915803F6 (THYMFET03), 3035012F6 (TLYMNOT05), SAFC00027F1, SAFC00254F1, SAFC02376F1, SAFC01609F1
23	54	3013946	MUSCNOT07	673753H1 (CRBLNOT01), 989218X11 and 989218X14 (LVENNOT03), 2821720F6 (ADRETUT06), 3013946F6, 3013946H1, and 3013946T6 (MUSCNOT07), 4693167H1 (BRAENOT02)
24	55	067967	HUVESTB01	067967X92, 067966R1, and 067967H1 (HUVESTB01), SAIA02074F1, SAIA03254F1, SAIA03603F1, and SAIA02259F1
25	56	346275	THYMNOT02	346275H1 (THYMNOT02), 609792X12 (COLNNOT01), SAGA03543F1, SAGA02528F1, and SAGA00285F1
26	57	283746	CARDNOT01	283746H1 and 283746X10 (CARDNOT01), 4903108H1 (TLYMNOT08), 557918X15 (MPHGLPT02), and 2379045F6 (ISLTNOT01)
27	58	2696537	UTRSNOT12	2696537H1 (UTRSNOT12), 3173337F6 (UTRSTUT04), 082658X100 (HUVESTB01), and 603219T6 (BRSTTUT01)

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
28	59	551178	BEPINOT01	551178H1 (BEPINOT01), 861522R1 (BRAITUT03), 965838R1 (BRSTNOT05), 1574007F1 and 1574007T1 (LNODNOT03), 1830083T6 and 1831194T6 (THP1AZT01), 3098496H1 (CERVNOT03), 3293481H1 (TLYJINT01)
29	60	619292	PGANNOT01	613165F1 (COLNTUT02), 619292H1 and 619292X13 (PGANNOT01)
30	61	2054049	BEPINOT01	1736355F6 (COLNNOT22), 2054049H1 (BEPINOT01), 2379092T6 (ISLTNOT01), 3127284T3 (LUNGTUT12), 3136377F6 (SMCCNOT01), SBMA00545F1, SBMA00827F1, SBMA02930F1, SBMA02853F1
31	62	2843910	DRGLNOT01	036294X71 (HUVENOB01), 066017X102, 068399R1, and 068399X3 (HUVESTB01), 1527276H1 (UCMCL5T01), 1846570T6 (COLNNOT09), 2843910H1 (DRGLNOT01)

TABLE 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
1	300	S3 S15 S19 S20 S24 T98 S125 S231 T238 S257 S282 S12 S41 S70 T120 T143 S146 T242	N85 N88 N96	Protein kinase motifs: G161-F256 catalytic tk domain IX: V180-E202	Protein kinase	BLAST PFAM PRINTS
2	147	S85 T38 S90		Calcium-binding repeat motifs: G28-L115	PKC-potentiated inhibitory protein of PP1 (CPI17)	BLAST PRINTS BLOCKS
3	431	T178 S282 T25 S34 S75 S106 S194 S198 T208 T264 S299 S303 S304 S308 T328 S345 S388 T46 S137 S260	N44 N242	PTK signatures: A18-Y283 ATP-binding site: I30-K53, E127-G164 Y196-H219 PK catalytic subdomains: M99-E112, Y134-L152 G181-I191, Y243-A265	Ste20-like protein kinase	BLOCKS PRINTS PROFILESCAN BLAST
4	218	S108 S68 S90 T133 T170 S172 T34 T123 T207		Phosphofructokinase domains: I47, V177-Q195 L148-Y164		PRINTS

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
5	474	S14 S89 S98 S132 S472 T22 S26 S62 S66 T204 T320 T345 T359 S427 S443 S94 S128 T211 T336 S443 Y155		Protein kinase family signature: Y144-F425	serine /threonine protein kinase	MOTIFS PFAM BLOCKS PRINTS ProfileScan BLAST
6	540	S102 S183 S267 T296 T301 S442 S34 S58 S180 S207 S224 T360 S374 S401 S428 S478 T484 Y23	N100 N391 N457 N537	Protein kinase family signature: L18-L287	serine /threonine protein kinase	MOTIFS PFAM BLOCKS PRINTS PROFILESCAN BLAST
7	454	S57 S69 S130 T203 T212 S338 S420 S91 T101 T220 S271 S295 T315 S359 S381 Y197	N55 N140 N218 N403 N437 N441	SH2 domain: W63-Y138, W354-Y428 PI 3 kinase P85 regulator: K153-G176, A216-N257, R287-N332	phosphatidyl-inositol 3-kinase	PFAM BLOCKS PRINTS BLAST
8	502	S246 T498 T21 S65 S76 T193 T203 S275 S312 S355 T484 S106 T222 S323 T498 Y347	N302 N414	Signal petide: M1-T21 SH2 domain: V70-E80 ER targeting signal: K499-L502	tyrosine kinase	SigPept BLOCKS MOTIFS BLAST

TABLE 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
9	281	T66 T140 T141 T182 S210	N117 N139	Signal peptide: M1-I76	calcium /calmodulin-dependent protein kinase	PFAM BLAST
10	510	T297 S323 S358 S51 T312 S323 T325 S329 T377 T390 T483 S24 S152 T201 S210 S247 T292 T406 T407	N185 N349 N381 N405	Protein kinase family signature: R52-V261	Serine /threonine protein kinase	PFAM BLOCKS PRINTS MOTIFS BLAST
11	248	S5 S20 S36 T210 T245	N208	Tyrosine specific phosphatase active site: F166-A220 Dual specificity phosphatase: H95-R240	Tyrosine phosphatase or Dual specificity phosphatase	BLAST, MOTIFS BLOCKS, PRINTS PROFILESCAN PFAM

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
12	810	S62 S290 T429 S758 T17 T104 S108 T216 S279 T316 S330 T360 S386 T405 S425 S465 T473 S497 T547 T561 T715 S733 S738 S768 S196 S222 S229 S267 T281 T321 T347 S370 T400 T512 S534 T609 S617 S663 S751 T754 T762 Y67	N33		Protein kinase	BLAST, MOTIFS
13	549	S6 T502 T21 T116 S125 S320 T417 S46 S87 T240 S390 S397 S405 S430 S497	N238	ATP/GTP-binding site (p-loop): G58-T65 Protein kinase signature: I176-K199 I292-L304 Y347-L370 F456-L483	Dual specificity tyrosine /serine protein kinase	BLAST, MOTIFS BLOCKS, PRINTS PFAM
14	416	S312 T20 T97 S104 S183 T185 T211 T274 S381 S411 S72 S79 S140 S318 Y53		SH3 domain: A366-D384 N402-E414	PEST phosphatase interacting protein	BLAST, MOTIFS BLOCKS, PRINTS PFAM

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
15	425	T34 S233 S234 S25 S107 T144 T198 T250 S251 S258 S282 S300 S324 S345 T390 T51 T133 S365 S383 Y71	N23 N176 N362		SH3 binding protein	BLAST, MOTIFS
16	1135	S77 T187 S259 S554 S815 S9 S17 T59 S112 T124 T222 S264 T319 S324 S326 S550 T572 S625 S681 S682 T688 T689 S706 S720 T931 S958 S978 S999 S255 T309 T351 T543 S550 S624 S632 S726 T811 S898 S1012 S1113 Y321 Y323 Y467	N33 N570 N718 N1067	Protein kinase signature: V31-K54 V149-L161 W129-V182 Tyrosine kinase catalytic site: G190-I200 S214-M236 NIK1-like kinase domain: Y836-R1115	NIK kinase	BLAST, MOTIFS PROFILESCAN BLOCKS, PRINTS PFAM
17	228	T163 S60 T78 T68 S88 S147	N19 N100 N114		Interferon-induced PK regulator (P52rIPK)	BLAST

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
18	503	S51 T262 T36 S79 T94 S109 T361 T362 T403 S472 T47 S334 S343 Y17	N313 N333 N360	Protein kinase signature: I20-K43 V132-L144 V195-E217 Protein kinase domain: Y14-V272	calcium /calmodulin-dependent protein kinase II, beta 3 isoform	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILESCAN
19	433	S12 S77 S124 S131 S255 S290 T327 S365 S402 T70 Y88			Choline kinase isolog 384D8_3	BLAST, MOTIFS
20	527	S417 S154 S199 T367 S453 T120 S178 S413 T447 S473	N470	Protein kinase signature: I144-K167 I260-V172 ATP-binding site: Q247-G284 Y318-F341 Protein kinase domain: I138-L427	MAP-related protein kinase	BLAST, BLOCKS MOTIFS, PFAM, PROFILESCAN

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
21	322	S19 S122 T198 T200 T236 S251 T260 S264 T301 S14 S52 T181 T225	N196 N249	Protein kinase signature: L163-I175 ATP-binding site: M150-V187 I224-H247 Protein kinase domain: S32-E316	Protein tyrosine kinase	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILESCAN
22	802	S70 T87 S750 T14 T98 S144 T150 S230 S263 T353 T465 T470 S517 S633 T751 S758 T27 T74 T100 T207 S268 S368 S458	N36 N655	Protein kinase signature: L55-K81, L432-K455 ATP-binding site: E160-G197, H232-F255 PTK catalytic domain: H534-F552, C603-H625 Protein kinase domains: F49-F318, L427-L687 Protein kinase C domain: Q319-I382	Ribosomal S6 protein kinase	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILESCAN
23	641	S51 T262 S398 S436 S479 T36 S79 T94 S109 T375 T376 T541 S610 T47 S315 S333 S342 S393 S422 S431 S465 S474 S508 Y17	N313 N332 N374	Protein kinase signature: I20-K43 V132-L144 ATP-binding site: Q119-A156 Y191-F214 Protein kinase domain: Y14-V272	Ca2+ /calmodulin dependent protein kinase	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILESCAN

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
24	588	S106 T155 S359 T388 T456 T531 T4, S58 S108 T126 S132 T279 S350 S436 S469 S508 S537 Y32	N63 N130 N574	Protein kinase catalytic domain: Y209-S445, F495-I522 ATP-binding site: I215-K238 STK core catalytic motif: I331-L343	Protein kinase Dyrk2	MOTIFS PFAM BLOCKS PRINTS BLAST
25	389	S31 T301 S56 S96 S134 T149 S186 S201 S283 S358 S375 Y148 Y165	N257 N343 N364	Protein kinase catalytic domain: E73-I311 STK core catalytic motif: I172-Y184 PTK core domain: D152-D208	CaM-like protein kinase	BLAST PFAM MOTIFS BLOCKS PRINTS PROFILESCAN
26	343	S68 S81 S137 S184 T219 S276 S297 T29 T125 Y86 Y211	N332	EF hand calcium-binding signature: D176-L188	protein phosphatase 2A (PR72)	BLAST MOTIFS BLOCKS
27	184	S36 T105 S40 S70 T117 Y50	N62	Tyrosine phosphatase active site domain: L63-V118	MAP kinase phosphatase (X17C)	BLAST PROFILESCAN BLOCKS PRINTS MOTIFS

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
28	367	S10 S21 S44 S103 T116 T267 T309 S191 S213 S218 S256 T305 S352 Y159 Y344	N16 N17		protein phosphatase 2A, A-subunit	BLAST
29	118	S34 S84	N43	Signal peptide: M1-A27 PDZ domain: H8-S73	tyrosine phosphatase	SPScan PFAM BLAST
30	356	S9 S94 T209 T220 S259 S337 S5 S26 S75 S121 T154 S282 S332 S339 Y15 Y84	N333	tyrosine-specific protein phosphatase active site: I108-K164	tyrosine phosphatase (myotubularin)	PROFILESCAN MOTIFS BLOCKS PRINTS BLAST
31	453	S38 S73 S119 S131 S193 S200 T236 S293 S341 T379 T124 S173 T214 S252 T256 S282 S302 S313 S391 S397	N43 N67 N357	protein phosphatase 2A p55 subunit: P10-K451	protein phosphatase 2A p55 regulatory subunit, alpha isoform	PFAM MOTIFS BLOCKS PRINTS BLAST

TABLE 3

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
32	Hematopoietic/Immune (0.333) Reproductive (0.333)	Cell proliferation (0.500) Inflammation (0.333)	PBLUESCRIPT
33	Nervous (0.216) Reproductive(0.235) Cardiovascular (0.118)	Cell proliferation (0.530) Inflammation (0.352)	pINCY
34	Reproductive (0.293) Gastrointestinal (0.192)	Cell proliferation (0.641) Inflammation (0.335)	pINCY
35	Reproductive (0.284) Nervous (0.210) Cardiovascular (0.1213)	Cell proliferation (0.729) Inflammation (0.272)	pINCY
36	Nervous (0.529) Developmental (0.118) Gastrointestinal (0.118)	Cell proliferation (0.588) Neurological (0.118) Inflammation (0.118)	pINCY
37	Hematopoietic/Immune (0.268) Reproductive (0.244) Nervous (0.122)	Inflammation (0.488) Cell Proliferative (0.415)	PBLUESCRIPT
38	Reproductive (0.400) Hematopoietic/Immune (0.160) Nervous (0.160)	Cell proliferation (0.600) Inflammation (0.320)	pINCY
39	Cardiovascular (0.312) Reproductive (0.312) Developmental (0.188)	Cell proliferation (0.938) Inflammation (0.125)	pINCY
40	Nervous (0.400) Gastrointestinal (0.267) Developmental (0.133)	Cell proliferation (0.733) Neurological (0.133) Inflammation (0.133)	pINCY
41	Gastrointestinal (0.267) Nervous (0.233) Reproductive (0.167)	Inflammation (0.533) Cell proliferation (0.534)	pSPORT1

Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
42	Musculoskeletal (0.500) Developmental (0.167) Gastrointestinal (0.167)	Cancer (0.834) Inflammation (0.167)	PBLUESCRIPT
43	Reproductive (0.240) Nervous (0.151) Gastrointestinal (0.135)	Cell proliferation (0.536) Inflammation (0.417)	pSPORT1
44	Hematopoietic/Immune (0.278) Nervous (0.222) Dermatologic (0.111)	Cell proliferation (0.444) Inflammation (0.389)	pINCY
45	Hematopoietic/Immune (0.500) Gastrointestinal (0.125) Nervous (0.125)	Inflammation (0.500) Cell proliferative (0.500)	PBLUESCRIPT
46	Nervous (0.220) Reproductive (0.213) Hematopoietic/Immune (0.140)	Cell proliferation (0.573) Inflammation (0.380)	pSPORT1
47	Hematopoietic/Immune (0.190) Gastrointestinal (0.165) Nervous (0.139)	Cell proliferation (0.582) Inflammation (0.354)	pSPORT1

Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
48	Nervous (0.333) Reproductive (0.333) Hematopoietic/Immune (0.111)	Cancer (0.444) Inflammation (0.222) Neurological (0.111)	PBLUESCRIPT
49	Nervous (0.724) Cardiovascular (0.103)	Inflammation (0.276) Cancer (0.241) Neurological (0.172)	pINCY
50	Reproductive (0.235) Hematopoietic/Immune (0.188) Gastrointestinal (0.129)	Cancer (0.447) Inflammation (0.282) Fetal (0.153)	pINCY
51	Nervous (0.368) Developmental (0.158) Gastrointestinal (0.105)	Cancer (0.368) Fetal (0.211) Inflammation (0.105)	pSPORT1
52	Cardiovascular (0.312) Hematopoietic/Immune (0.312) Reproductive (0.158)	Fetal (0.688) Cancer (0.421) Inflammation (0.125)	pINCY
53	Reproductive (0.412) Nervous (0.235) Developmental (0.118)	Cancer (0.471) Fetal (0.235) Inflammation (0.235)	pINCY
54	Nervous (0.714) Cardiovascular (0.107)	Cancer (0.250) Inflammation (0.250) Neurological (0.179)	pINCY

Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	PBLUESCRIPT
55	Reproductive (0.533) Nervous (0.133)	Cell proliferation (0.601) Inflammation (0.270)	PBLUESCRIPT
56	Hematopoietic/Immune (0.278) Nervous (0.222) Reproductive (0.154)	Cell proliferation (0.388) Inflammation (0.333) Neurological (0.111)	PBLUESCRIPT
57	Hematopoietic/Immune (0.211) Cardiovascular (0.193) Nervous (0.175)	Cell proliferation (0.474) Inflammation (0.491)	PBLUESCRIPT
58	Reproductive (0.286) Cardiovascular (0.229) Musculoskeletal (0.143)	Cell proliferation (0.715) Inflammation (0.200)	pINCY
59	Reproductive (0.253) Gastrointestinal (0.211) Nervous (0.147)	Cancer and Cell proliferation (0.684) Inflammation and Immune Response (0.242)	pSPORT1
60	Nervous (0.667) Reproductive (0.333)	Cancer (1.000)	pSPORT1
61	Reproductive (0.357) Cardiovascular (0.179) Nervous (0.125)	Cancer and Cell proliferation (0.642) Inflammation and Immune Response (0.232)	pSPORT1
62	Nervous (0.228) Reproductive (0.175) Cardiovascular (0.158) Hematopoietic/Immune (0.158)	Cancer (0.368) Inflammation and Immune Response (0.263) Fetal (0.211)	pINCY

TABLE 4

Polynucleotide SEQ ID NO:	Library	Library Comment
32	BMARNOT02	Library was constructed using RNA isolated from the bone marrow of 24 male and female Caucasian donors, 16 to 70 years old.
33	SININOT01	Library was constructed using RNA isolated from ileum tissue removed from the small intestine of a 4-year-old Caucasian female, who died from a closed head injury. Patient history included jaundice as a baby. Previous surgeries included a double hernia repair
34	SPLNFET02	Library was constructed using RNA isolated from spleen tissue removed from a Caucasian male fetus, who died at 23 weeks' gestation from premature birth. Family history included diabetes.
35	OVARTUT02	Library was constructed using RNA isolated from ovarian tumor tissue removed from a 51-year-old Caucasian female during an exploratory laparotomy, total abdominal hysterectomy, salpingo-oophorectomy, and an incidental appendectomy. Pathology indicated mucinous cystadenoma presenting as a multiloculated neoplasm involving the entire left ovary. The right ovary contained a follicular cyst and a hemorrhagic corpus luteum. The uterus showed proliferative endometrium and a single intramural leiomyoma. The peritoneal biopsy indicated benign glandular inclusions consistent with endosalpingiosis. The patient presented with abnormal weight gain and ascites. Patient history included depressive disorder, joint pain, allergies, alcohol use, and a normal delivery. Family history included atherosclerotic coronary artery disease, benign hypertension, breast cancer and uterine cancer.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
36	PANCTUT01	library was constructed using RNA isolated from pancreatic tumor tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, and benign neoplasm in the large bowel. Previous surgeries included a total splenectomy, cholecystectomy, and abdominal hysterectomy. Family history included cardiovascular disease, type II diabetes, and stomach cancer.
37	SMCBUNT01	library was constructed using RNA isolated from bronchial smooth muscle cell tissue removed from a 21-year-old Caucasian male.
38	UTRSTUT05	Library was constructed using RNA isolated from uterine tumor tissue removed from a 41-year-old Caucasian female during a vaginal hysterectomy with dilation and curettage. Pathology indicated uterine leiomyoma. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Patient history included a ventral hernia and a benign ovarian neoplasm.
39	UTRSTUT04	library was constructed using RNA isolated from uterine tumor tissue removed from a 34-year-old Caucasian female during a hysteroscopy and an exploratory laparotomy with dilation and curettage. Pathology indicated an endometrial polyp, subserosal leiomyoma, and fragments of leiomyoma. Family history included hyperlipidemia, depressive disorder, benign hypertension, cerebrovascular disease, arteriosclerotic cardiovascular disease, and type II diabetes.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
40	SMCBUNT01	library was constructed using RNA isolated from bronchial smooth muscle cell tissue removed from a 21-year-old Caucasian male.
41	ADRENOT03	library was constructed using RNA isolated from the adrenal tissue of a 17-year-old Caucasian male, who died from cerebral anoxia.
42	TESTNOT04	library was constructed using RNA isolated from testicular tissue removed from a 37-year-old Caucasian male who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
43	BRSTTUT01	library was constructed using RNA isolated from breast tumor tissue removed from a 55-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated invasive grade 4 mammary adenocarcinoma of mixed lobular and ductal type, extensively involving the left breast. The tumor was identified in the deep dermis near the lactiferous ducts with extracapsular extension. Seven mid and low and five high axillary lymph nodes were positive for tumor. Proliferative fibrocysytic changes were characterized by apocrine metaplasia, sclerosing adenosis, cyst formation, and ductal hyperplasia without atypia. Patient history included atrial tachycardia, blood in the stool, and a benign breast neoplasm. Family history included benign hypertension, atherosclerotic coronary artery disease, cerebrovascular disease, and depressive disorder.
44	LUNGNOT10	library was constructed using RNA isolated from the lung tissue of a Caucasian male fetus who died at 23 weeks' gestation.
45	UCMCL5T01	library was constructed using RNA isolated from mononuclear cells obtained from the umbilical cord blood of 12 individuals. The cells were cultured for 12 days with IL-5 before RNA was isolated from the pooled lysates.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
46	BRSTTUT03	library was constructed using RNA isolated from breast tumor tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated multicentric invasive grade 4 lobular carcinoma. The mass was identified in the upper outer quadrant, and three separate nodules were found in the lower outer quadrant of the left breast. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular disease, coronary artery aneurysm, breast cancer, prostate cancer, atherosclerotic coronary artery disease, and type I diabetes.
47	BRSTNOT05	library was constructed using RNA isolated from breast tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated multicentric invasive grade 4 lobular carcinoma. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular and cardiovascular disease, breast and prostate cancer, and type I diabetes.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
48	SPLNNOT02	The library was constructed using RNA isolated from the spleen tissue of a 29-year-old Caucasian male, who died from head trauma. Serologies were positive for cytomegalovirus (CMV). Patient history included alcohol, marijuana, and tobacco use.
49	BRAITUT08	The library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 47-year-old Caucasian male during excision of cerebral meningeal tissue. Pathology indicated grade 4 fibrillary astrocytoma with focal tumoral radionecrosis. Patient history included cerebrovascular disease, deficiency anemia, hyperlipidemia, epilepsy, and tobacco use. Family history included cerebrovascular disease and a malignant prostate neoplasm.
50	PANCTUT01	The library was constructed using RNA isolated from pancreatic tumor tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, benign neoplasm in the large bowel, and a cataract. Previous surgeries included a total splenectomy, cholecystectomy, and abdominal hysterectomy. Family history included cardiovascular disease, type II diabetes, and stomach cancer.
51	BRAITUT02	The library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
52	THP1NOT03	The library was constructed using RNA isolated from untreated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
53	BRSTNOT12	The library was constructed using RNA isolated from diseased breast tissue removed from a 32-year-old Caucasian female during a bilateral reduction mammoplasty. Pathology indicated nonproliferative fibrocystic disease. Family history included cardiovascular disease.
54	MUSCNOT07	The library was constructed using RNA isolated from muscle tissue removed from the forearm of a 38-year-old Caucasian female during a soft tissue excision. Pathology for the associated tumor tissue indicated intramuscular hemangioma. Family history included breast cancer, benign hypertension, cerebrovascular disease, colon cancer, and type II diabetes.
55	HUVESTB01	Library was constructed using RNA isolated from shear-stressed HUV-EC-C (ATCC CRL 1730) cells. HUV-EC-C is an endothelial cell line derived from the vein of a normal human umbilical cord (ref:PNAS 81:6413).
56	THYMNOT02	ibrary was constructed using polyA RNA isolated from thymus tissue removed from a 3-year-old Caucasian male, who died from drowning.
57	CARDNOT01	Library was constructed using RNA isolated from the cardiac muscle of a 65-year-old Caucasian male, who died from a self-inflicted gunshot wound.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
58	UTRSNOT12	Library was constructed using RNA isolated from uterine myometrial tissue removed from a 41-year-old Caucasian female during a vaginal hysterectomy with a dilatation and curettage. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Pathology for the associated tumor tissue indicated uterine leiomyoma. The patient presented with an unspecified menstrual disorder. Patient history included ventral hernia, normal delivery, a benign ovarian neoplasm, and tobacco abuse. Previous surgeries included a bilateral destruction of fallopian tubes, removal of a solitary ovary, and an exploratory laparotomy.
59	BEPINOT01	Library was constructed using RNA isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male.
60	PGANNOT01	Library was constructed using RNA isolated from paraganglionic tumor tissue removed from the intra-abdominal region of a 46-year-old Caucasian male during exploratory laparotomy. Pathology indicated a benign paraganglioma and association with a grade 2 renal cell carcinoma, clear cell type.
61	BEPINOT01	Library was constructed using RNA isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male.
62	DRGLNOT01	Library was constructed using RNA isolated from dorsal root ganglion tissue removed from the low thoracic/high lumbar region of a 32-year- old Caucasian male who died from acute pulmonary edema and bronchopneumonia, bilateral pleural and pericardial effusions, and malignant lymphoma (natural killer cell type). Patient history included probable cytomegalovirus infection, hepatic congestion and steatosis, splenomegaly, hemorrhagic cystitis, thyroid hemorrhage, and Bell's palsy.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	*ESTs:* Probability value= 1.0E-8 or less *Full Length sequences*: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	*ESTs:* fasta E value=1.06E-6 *Assembled ESTs*: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less *Full Length sequences:* fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score≥GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. supra; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.

3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.

4. An isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide of claim 3.

5. An isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide of claim 3.

6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.

7. A method for detecting a polynucleotide, the method comprising the steps of:

(a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and

(b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.

8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.

9. An isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:32-62 and fragments thereof.

10. An isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide of claim 9.

11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.

12. An expression vector comprising at least a fragment of the polynucleotide of claim 3.

13. A host cell comprising the expression vector of claim 12.

14. A method for producing a polypeptide, the method comprising the steps of:

a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and

b) recovering the polypeptide from the host cell culture.

15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.

16. A purified antibody which specifically binds to the polypeptide of claim 1.

17. A purified agonist of the polypeptide of claim 1.

18. A purified antagonist of the polypeptide of claim 1.

19. A method for treating or preventing a disorder associated with decreased expression or activity of PHSP, the method comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition of claim 15.

20. A method for treating or preventing a disorder associated with increased expression or activity of PHSP, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

SEQUENCE LISTING

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HILLMAN, Jennifer L.
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TANG, Y. Tom
CORLEY, Neil C.
GUEGLER, Karl J.
BAUGHN, Mariah R.
PATTERSON, Chandra
BANDMAN, Olga
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Thr Glu Gln Phe Asn Gln Leu His Asn Arg Arg Asn Glu Asn Leu
                35                  40                  45
Gln Leu Gly Pro Leu Gly Arg Asp Pro Pro Gln Glu Cys Ser Thr
                50                  55                  60
Phe Ser Pro Thr Asp Ser Gly Glu Glu Pro Gly Gln Leu Ser Pro
                65                  70                  75
Gly Val Gln Phe Gln Arg Arg Gln Asn Gln Arg Arg Phe Ser Met
                80                  85                  90
Glu Asp Val Ser Lys Arg Leu Ser Leu Pro Met Asp Ile Arg Leu
                95                 100                 105
Pro Gln Glu Phe Leu Gln Lys Leu Gln Met Glu Ser Pro Asp Leu
                110                 115                 120
Pro Lys Pro Leu Ser Arg Met Ser Arg Arg Ala Ser Leu Ser Asp
                125                 130                 135
Ile Gly Phe Gly Lys Leu Glu Thr Tyr Val Lys Leu Asp Lys Leu
                140                 145                 150
Gly Glu Gly Thr Tyr Ala Thr Val Phe Lys Gly Arg Ser Lys Leu
                155                 160                 165
Thr Glu Asn Leu Val Ala Leu Lys Glu Ile Arg Leu Glu His Glu
                170                 175                 180
Glu Gly Ala Pro Cys Thr Ala Ile Arg Glu Val Ser Leu Leu Lys
                185                 190                 195
Asn Leu Lys His Ala Asn Ile Val Thr Leu His Asp Leu Ile His
                200                 205                 210
Thr Asp Arg Ser Leu Thr Leu Val Phe Glu Tyr Leu Asp Ser Asp
                215                 220                 225
Leu Lys Gln Tyr Leu Asp His Cys Gly Asn Leu Met Ser Met His
                230                 235                 240
Asn Val Lys Ile Phe Met Phe Gln Leu Leu Arg Gly Leu Ala Tyr
                245                 250                 255
Cys His His Arg Lys Ile Leu His Arg Asp Leu Lys Pro Gln Asn
                260                 265                 270
Leu Leu Ile Asn Glu Arg Gly Glu Leu Lys Leu Ala Asp Phe Gly
                275                 280                 285
```

Leu Ala Arg Ala Lys Ser Val Pro Thr Lys Thr Tyr Ser Asn Glu
290 295 300
Val Val Thr Leu Trp Tyr Arg Pro Pro Asp Val Leu Leu Gly Ser
305 310 315
Thr Glu Tyr Ser Thr Pro Ile Asp Met Trp Gly Val Gly Cys Ile
320 325 330
His Tyr Glu Met Ala Thr Gly Arg Pro Leu Phe Pro Gly Ser Thr
335 340 345
Val Lys Glu Glu Leu His Leu Ile Phe Arg Leu Leu Gly Thr Pro
350 355 360
Thr Glu Glu Thr Trp Pro Gly Val Thr Ala Phe Ser Glu Phe Arg
365 370 375
Thr Tyr Ser Phe Pro Cys Tyr Leu Pro Gln Pro Leu Ile Asn His
380 385 390
Ala Pro Arg Leu Asp Thr Asp Gly Ile His Leu Leu Ser Ser Leu
395 400 405
Leu Leu Tyr Glu Ser Lys Ser Arg Met Ser Ala Glu Ala Ala Leu
410 415 420
Ser His Ser Tyr Phe Arg Ser Leu Gly Glu Arg Val His Gln Leu
425 430 435
Glu Asp Thr Ala Ser Ile Phe Ser Leu Lys Glu Ile Gln Leu Gln
440 445 450
Lys Asp Pro Gly Tyr Arg Gly Leu Ala Phe Gln Gln Pro Gly Arg
455 460 465
Gly Lys Asn Arg Arg Gln Ser Ile Phe
470

<210> 6
<211> 540
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 156108

<400> 6
Met Asn Gly Glu Ala Ile Cys Ser Ala Leu Pro Thr Ile Pro Tyr
1 5 10 15
His Lys Leu Ala Asp Leu Arg Tyr Leu Ser Arg Gly Ala Ser Gly
20 25 30
Thr Val Ser Ser Ala Arg His Ala Asp Trp Arg Val Gln Val Ala
35 40 45
Val Lys His Leu His Ile His Thr Pro Leu Leu Asp Ser Glu Arg
50 55 60
Lys Asp Val Leu Arg Glu Ala Glu Ile Leu His Lys Ala Arg Phe
65 70 75
Ser Tyr Ile Leu Pro Ile Leu Gly Ile Cys Asn Glu Pro Glu Phe
80 85 90
Leu Gly Ile Val Thr Glu Tyr Met Pro Asn Gly Ser Leu Asn Glu
95 100 105
Leu Leu His Arg Lys Thr Glu Tyr Pro Asp Val Ala Trp Pro Leu
110 115 120
Arg Phe Arg Ile Leu His Glu Ile Ala Leu Gly Val Asn Tyr Leu

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                125                 130                 135
His Asn Met Thr Pro Pro Leu Leu His His Asp Leu Lys Thr Gln
                140                 145                 150
Asn Ile Leu Leu Asp Asn Glu Phe His Val Lys Ile Ala Asp Phe
                155                 160                 165
Gly Leu Ser Lys Trp Arg Met Met Ser Leu Ser Gln Ser Arg Ser
                170                 175                 180
Ser Lys Ser Ala Pro Glu Gly Gly Thr Ile Ile Tyr Met Pro Pro
                185                 190                 195
Glu Asn Tyr Glu Pro Gly Gln Lys Ser Arg Ala Ser Ile Lys His
                200                 205                 210
Asp Ile Tyr Ser Tyr Ala Val Ile Thr Trp Glu Val Leu Ser Arg
                215                 220                 225
Lys Gln Pro Phe Glu Asp Val Thr Asn Pro Leu Gln Ile Met Tyr
                230                 235                 240
Ser Val Ser Gln Gly His Arg Pro Val Ile Asn Glu Glu Ser Leu
                245                 250                 255
Pro Tyr Asp Ile Pro His Arg Ala Arg Met Ile Ser Leu Ile Glu
                260                 265                 270
Ser Gly Trp Ala Gln Asn Pro Asp Glu Arg Pro Ser Phe Leu Lys
                275                 280                 285
Cys Leu Ile Glu Leu Glu Pro Val Leu Arg Thr Phe Glu Glu Ile
                290                 295                 300
Thr Phe Leu Glu Ala Val Ile Gln Leu Lys Lys Thr Lys Leu Gln
                305                 310                 315
Ser Val Ser Ser Ala Ile His Leu Cys Asp Lys Lys Lys Met Glu
                320                 325                 330
Leu Ser Leu Asn Ile Pro Val Asn His Gly Pro Gln Glu Glu Ser
                335                 340                 345
Cys Gly Ser Ser Gln Leu His Glu Asn Ser Gly Ser Pro Glu Thr
                350                 355                 360
Ser Arg Ser Leu Pro Ala Pro Gln Asp Asn Asp Phe Leu Ser Arg
                365                 370                 375
Lys Ala Gln Asp Cys Tyr Phe Met Lys Leu His His Cys Pro Gly
                380                 385                 390
Asn His Ser Trp Asp Ser Thr Ile Ser Gly Ser Gln Arg Ala Ala
                395                 400                 405
Phe Cys Asp His Lys Thr Thr Pro Cys Ser Ser Ala Ile Ile Asn
                410                 415                 420
Pro Leu Ser Thr Ala Gly Asn Ser Glu Arg Leu Gln Pro Gly Ile
                425                 430                 435
Ala Gln Gln Trp Ile Gln Ser Lys Arg Glu Asp Ile Val Asn Gln
                440                 445                 450
Met Thr Glu Ala Cys Leu Asn Gln Ser Leu Asp Ala Leu Leu Ser
                455                 460                 465
Arg Asp Leu Ile Met Lys Glu Asp Tyr Glu Leu Val Ser Thr Lys
                470                 475                 480
Pro Thr Arg Thr Ser Lys Val Arg Gln Leu Leu Asp Thr Thr Asp
                485                 490                 495
Ile Gln Gly Glu Glu Phe Ala Lys Val Ile Val Gln Lys Leu Lys
                500                 505                 510
Asp Asn Lys Gln Met Gly Leu Gln Pro Tyr Pro Glu Ile Leu Val
                515                 520                 525
Val Ser Arg Ser Pro Ser Leu Asn Leu Leu Gln Asn Lys Ser Met
                530                 535                 540
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<210> 7
<211> 454
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 2883243

<400> 7
Met Tyr Asn Thr Val Trp Asn Met Glu Asp Leu Asp Leu Glu Tyr
 1               5                  10                  15
Ala Lys Thr Asp Ile Asn Cys Gly Thr Asp Leu Met Phe Tyr Ile
                20                  25                  30
Glu Met Asp Pro Pro Ala Leu Pro Pro Lys Pro Pro Lys Pro Thr
                35                  40                  45
Thr Val Ala Asn Asn Gly Met Asn Asn Asn Met Ser Leu Gln Asp
                50                  55                  60
Ala Glu Trp Tyr Trp Gly Asp Ile Ser Arg Glu Glu Val Asn Glu
                65                  70                  75
Lys Leu Arg Asp Thr Ala Asp Gly Thr Phe Leu Val Arg Asp Ala
                80                  85                  90
Ser Thr Lys Met His Gly Asp Tyr Thr Leu Thr Leu Arg Lys Gly
                95                 100                 105
Gly Asn Asn Lys Leu Ile Lys Ile Phe His Arg Asp Gly Lys Tyr
               110                 115                 120
Gly Phe Ser Asp Pro Leu Thr Phe Ser Ser Val Val Glu Leu Ile
               125                 130                 135
Asn His Tyr Arg Asn Glu Ser Leu Ala Gln Tyr Asn Pro Lys Leu
               140                 145                 150
Asp Val Lys Leu Leu Tyr Pro Val Ser Lys Tyr Gln Gln Asp Gln
               155                 160                 165
Val Val Lys Glu Asp Asn Ile Glu Ala Val Gly Lys Lys Leu His
               170                 175                 180
Glu Tyr Asn Thr Gln Phe Gln Glu Lys Ser Arg Glu Tyr Asp Arg
               185                 190                 195
Leu Tyr Glu Glu Tyr Thr Arg Thr Ser Gln Glu Ile Gln Met Lys
               200                 205                 210
Arg Thr Ala Ile Glu Ala Phe Asn Glu Thr Ile Lys Ile Phe Glu
               215                 220                 225
Glu Gln Cys Gln Thr Gln Glu Arg Tyr Ser Lys Glu Tyr Ile Glu
               230                 235                 240
Lys Phe Lys Arg Glu Gly Asn Glu Lys Glu Ile Gln Arg Ile Met
               245                 250                 255
His Asn Tyr Asp Lys Leu Lys Ser Arg Ile Ser Glu Ile Ile Asp
               260                 265                 270
Ser Arg Arg Arg Leu Glu Glu Asp Leu Lys Lys Gln Ala Ala Glu
               275                 280                 285
Tyr Arg Glu Ile Asp Lys Arg Met Asn Ser Ile Lys Pro Asp Leu
               290                 295                 300
Ile Gln Leu Arg Lys Thr Arg Asp Gln Tyr Leu Met Trp Leu Thr
               305                 310                 315
Gln Lys Gly Val Arg Gln Lys Lys Leu Asn Glu Trp Leu Gly Asn
               320                 325                 330
Glu Asn Thr Glu Asp Gln Tyr Ser Leu Val Glu Asp Asp Glu Asp
               335                 340                 345
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Leu Pro His His Asp Glu Lys Thr Trp Asn Val Gly Ser Ser Asn
                350                 355                 360
Arg Asn Lys Ala Glu Asn Leu Leu Arg Gly Lys Arg Asp Gly Thr
                365                 370                 375
Phe Leu Val Arg Glu Ser Ser Lys Gln Gly Cys Tyr Ala Cys Ser
                380                 385                 390
Val Val Val Asp Gly Glu Val Lys His Cys Val Ile Asn Lys Thr
                395                 400                 405
Ala Thr Gly Tyr Gly Phe Ala Glu Pro Tyr Asn Leu Tyr Ser Ser
                410                 415                 420
Leu Lys Glu Leu Val Leu His Tyr Gln His Thr Ser Leu Val Gln
                425                 430                 435
His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr Pro Val Tyr Ala
                440                 445                 450
Gln Gln Arg Arg


<210> 8
<211> 502
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 3173355

<400> 8
Met Phe Gly Thr Leu Leu Leu Tyr Cys Phe Phe Leu Ala Thr Val
  1               5                  10                  15
Pro Ala Leu Ala Glu Thr Gly Gly Glu Arg Gln Leu Ser Pro Glu
                 20                  25                  30
Lys Ser Glu Ile Trp Gly Pro Gly Leu Lys Ala Asp Val Val Leu
                 35                  40                  45
Pro Ala Arg Tyr Phe Tyr Ile Gln Ala Val Asp Thr Ser Gly Asn
                 50                  55                  60
Lys Phe Thr Ser Ser Pro Gly Glu Lys Val Phe Gln Val Lys Val
                 65                  70                  75
Ser Ala Pro Glu Glu Gln Phe Thr Arg Val Gly Val Gln Val Leu
                 80                  85                  90
Asp Arg Lys Asp Gly Ser Phe Ile Val Arg Tyr Arg Met Tyr Ala
                 95                 100                 105
Ser Tyr Lys Asn Leu Lys Val Glu Ile Lys Phe Gln Gly Gln His
                110                 115                 120
Val Ala Lys Ser Pro Tyr Ile Leu Lys Gly Pro Val Tyr His Glu
                125                 130                 135
Asn Cys Asp Cys Pro Leu Gln Asp Ser Ala Ala Trp Leu Arg Glu
                140                 145                 150
Met Asn Cys Pro Glu Thr Ile Ala Gln Ile Gln Arg Asp Leu Ala
                155                 160                 165
His Phe Pro Ala Val Asp Pro Glu Lys Ile Ala Val Glu Ile Pro
                170                 175                 180
Lys Arg Phe Gly Gln Arg Gln Ser Leu Cys His Tyr Thr Leu Lys
                185                 190                 195
Asp Asn Lys Val Tyr Ile Lys Thr His Gly Glu His Val Gly Phe
                200                 205                 210
Arg Ile Phe Met Asp Ala Ile Leu Leu Ser Leu Thr Arg Lys Val
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                215                     220                     225
Lys Met Pro Asp Val Glu Leu Phe Val Asn Leu Gly Asp Trp Pro
                230                     235                     240
Leu Glu Lys Lys Lys Ser Asn Ser Asn Ile His Pro Ile Phe Ser
                245                     250                     255
Trp Cys Gly Ser Thr Asp Ser Lys Asp Ile Val Met Pro Thr Tyr
                260                     265                     270
Asp Leu Thr Asp Ser Val Leu Glu Thr Met Gly Arg Val Ser Leu
                275                     280                     285
Asp Met Met Ser Val Gln Ala Asn Thr Gly Pro Pro Trp Glu Ser
                290                     295                     300
Lys Asn Ser Thr Ala Val Trp Arg Gly Arg Asp Ser Arg Lys Glu
                305                     310                     315
Arg Leu Glu Leu Val Lys Leu Ser Arg Lys His Pro Glu Leu Ile
                320                     325                     330
Asp Ala Ala Phe Thr Asn Phe Phe Phe Phe Lys His Asp Glu Asn
                335                     340                     345
Leu Tyr Gly Pro Ile Val Lys His Ile Ser Phe Phe Asp Phe Phe
                350                     355                     360
Lys His Lys Tyr Gln Ile Asn Ile Asp Gly Thr Val Ala Ala Tyr
                365                     370                     375
Arg Leu Pro Tyr Leu Leu Val Gly Asp Ser Val Val Leu Lys Gln
                380                     385                     390
Asp Ser Ile Tyr Tyr Glu His Phe Tyr Asn Glu Leu Gln Pro Trp
                395                     400                     405
Lys His Tyr Ile Pro Val Lys Ser Asn Leu Ser Asp Leu Leu Glu
                410                     415                     420
Lys Leu Lys Trp Ala Lys Asp His Asp Glu Glu Ala Lys Lys Ile
                425                     430                     435
Ala Lys Ala Gly Gln Glu Phe Ala Arg Asn Asn Leu Met Gly Asp
                440                     445                     450
Asp Ile Phe Cys Tyr Tyr Phe Lys Leu Phe Gln Glu Tyr Ala Asn
                455                     460                     465
Leu Gln Val Ser Glu Pro Gln Ile Arg Glu Gly Met Lys Arg Val
                470                     475                     480
Glu Pro Gln Thr Glu Asp Asp Leu Phe Pro Cys Thr Cys His Arg
                485                     490                     495
Lys Lys Thr Lys Asp Glu Leu
                500

<210> 9
<211> 282
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number:  5116906

<400> 9
Met Trp Ala Cys Gly Val Ile Leu Tyr Ile Leu Leu Val Gly Tyr
 1              5                   10                  15
Pro Pro Phe Trp Asp Glu Asp Gln His Arg Leu Tyr Gln Gln Ile
                20                  25                  30
Lys Ala Gly Ala Tyr Asp Phe Pro Ser Pro Glu Trp Asp Thr Val
                35                  40                  45
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Thr Pro Glu Ala Lys Asp Leu Ile Asn Lys Met Leu Thr Ile Asn
                50                  55                  60
Pro Ala Lys Arg Ile Thr Ala Ser Glu Ala Leu Lys His Pro Trp
                65                  70                  75
Ile Cys Gln Arg Ser Thr Val Ala Ser Met Met His Arg Gln Glu
                80                  85                  90
Thr Val Asp Cys Leu Lys Lys Phe Asn Ala Arg Arg Lys Leu Lys
                95                 100                 105
Gly Ala Ile Leu Thr Thr Met Leu Ala Thr Arg Asn Phe Ser Ala
               110                 115                 120
Ala Lys Ser Leu Leu Lys Lys Pro Asp Gly Val Lys Glu Ser Thr
               125                 130                 135
Glu Ser Ser Asn Thr Thr Ile Glu Asp Glu Asp Val Lys Ala Arg
               140                 145                 150
Lys Gln Glu Ile Ile Lys Val Thr Glu Gln Leu Ile Glu Ala Ile
               155                 160                 165
Asn Asn Gly Asp Phe Glu Ala Tyr Thr Lys Ile Cys Asp Pro Gly
               170                 175                 180
Leu Thr Ala Phe Glu Pro Glu Ala Leu Gly Asn Leu Val Glu Gly
               185                 190                 195
Met Asp Phe His Arg Phe Tyr Phe Glu Asn Ala Leu Ser Lys Ser
               200                 205                 210
Asn Lys Pro Ile His Thr Ile Ile Leu Asn Pro His Val His Leu
               215                 220                 225
Val Gly Asp Asp Ala Ala Cys Ile Ala Tyr Ile Arg Leu Thr Gln
               230                 235                 240
Tyr Met Asp Gly Ser Gly Met Pro Lys Thr Met Gln Ser Glu Glu
               245                 250                 255
Thr Arg Val Trp His Arg Arg Asp Gly Lys Trp Gln Asn Val His
               260                 265                 270
Phe His Arg Ser Gly Ser Pro Thr Val Pro Ile Asn
               275                 280


&lt;210&gt; 10
&lt;211&gt; 510
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;220&gt;
&lt;221&gt; misc_feature
&lt;223&gt; Incyte Clone Number: 940589

&lt;400&gt; 10
Met Lys Ala Asp Ile Lys Ile Trp Ile Leu Thr Gly Asp Lys Gln
  1               5                  10                  15
Glu Thr Ala Ile Asn Ile Gly His Ser Cys Lys Leu Leu Lys Lys
                 20                  25                  30
Asn Met Gly Met Ile Val Ile Asn Glu Gly Ser Leu Asp Ser Phe
                 35                  40                  45
Ser Asn Thr Gln Asn Ser Arg Lys Glu Ala Val Leu Leu Ala Lys
                 50                  55                  60
Met Lys His Pro Asn Ile Val Ala Phe Lys Glu Ser Phe Glu Ala
                 65                  70                  75
Glu Gly His Leu Tyr Ile Val Met Glu Tyr Cys Asp Gly Gly Asp
                 80                  85                  90
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Leu Met Gln Lys Ile Lys Gln Gln Lys Gly Lys Leu Phe Pro Glu
95 100 105
Asp Met Ile Leu Asn Trp Phe Thr Gln Met Cys Leu Gly Val Asn
110 115 120
His Ile His Lys Lys Arg Val Leu His Arg Asp Ile Lys Ser Lys
125 130 135
Asn Ile Phe Leu Thr Gln Asn Gly Lys Val Lys Leu Gly Asp Phe
140 145 150
Gly Ser Ala Arg Leu Leu Ser Asn Pro Met Ala Phe Ala Cys Thr
155 160 165
Tyr Val Gly Thr Pro Tyr Tyr Val Pro Pro Glu Ile Trp Glu Asn
170 175 180
Leu Pro Tyr Asn Asn Lys Ser Asp Ile Trp Ser Leu Gly Cys Ile
185 190 195
Leu Tyr Glu Leu Cys Thr Leu Lys His Pro Phe Gln Ala Asn Ser
200 205 210
Trp Lys Asn Leu Ile Leu Lys Val Cys Gln Gly Cys Ile Ser Pro
215 220 225
Leu Pro Ser His Tyr Ser Tyr Glu Leu Gln Phe Leu Val Lys Gln
230 235 240
Met Phe Lys Arg Asn Pro Ser His Arg Pro Ser Ala Thr Thr Leu
245 250 255
Leu Ser Arg Gly Ile Val Ala Arg Leu Val Gln Lys Cys Leu Pro
260 265 270
Pro Glu Ile Ile Met Glu Tyr Gly Glu Glu Val Leu Glu Glu Ile
275 280 285
Lys Asn Ser Lys His Asn Thr Pro Arg Lys Lys Thr Asn Pro Ser
290 295 300
Arg Ile Arg Ile Ala Leu Gly Asn Glu Ala Ser Thr Val Gln Glu
305 310 315
Glu Glu Gln Asp Arg Lys Gly Ser His Thr Asp Leu Glu Ser Ile
320 325 330
Asn Glu Asn Leu Val Glu Ser Ala Leu Arg Arg Val Asn Arg Glu
335 340 345
Glu Lys Gly Asn Lys Ser Val His Leu Arg Lys Ala Ser Ser Pro
350 355 360
Asn Leu His Arg Arg Gln Trp Glu Lys Asn Val Pro Asn Thr Ala
365 370 375
Leu Thr Ala Leu Glu Asn Ala Ser Ile Leu Thr Ser Ser Leu Thr
380 385 390
Ala Glu Asp Asp Arg Gly Gly Ser Val Ile Lys Tyr Ser Lys Asn
395 400 405
Thr Thr Arg Lys Gln Trp Leu Lys Glu Thr Pro Asp Thr Leu Leu
410 415 420
Asn Ile Leu Lys Asn Ala Asp Leu Ser Leu Ala Phe Gln Thr Tyr
425 430 435
Thr Ile Tyr Arg Pro Gly Ser Glu Gly Phe Leu Lys Gly Pro Leu
440 445 450
Ser Glu Glu Thr Glu Ala Ser Asp Ser Val Asp Gly Gly His Asp
455 460 465
Ser Val Ile Leu Asp Pro Glu Arg Leu Glu Pro Gly Leu Asp Glu
470 475 480
Glu Asp Thr Asp Phe Glu Glu Glu Asp Asp Asn Pro Asp Trp Val
485 490 495
Ser Glu Leu Lys Lys Arg Ala Gly Trp Gln Gly Leu Cys Asp Arg
500 505 510

<210> 11
<211> 248
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 304421

<400> 11
Met Ala Glu Thr Ser Leu Pro Glu Leu Gly Gly Glu Asp Lys Ala
1 5 10 15
Thr Pro Cys Pro Ser Ile Leu Glu Leu Glu Glu Leu Leu Arg Ala
20 25 30
Gly Lys Ser Ser Cys Ser Arg Val Asp Glu Val Trp Pro Asn Leu
35 40 45
Phe Ile Gly Asp Ala Met Asp Ser Leu Gln Lys Gln Asp Leu Arg
50 55 60
Arg Pro Lys Ile His Gly Ala Val Gln Ala Ser Pro Tyr Gln Pro
65 70 75
Pro Thr Leu Ala Ser Leu Gln Arg Leu Leu Trp Val Arg Gln Ala
80 85 90
Ala Thr Leu Asn His Ile Asp Glu Val Trp Pro Ser Leu Phe Leu
95 100 105
Gly Asp Ala Tyr Ala Ala Arg Asp Lys Ser Lys Leu Ile Gln Leu
110 115 120
Gly Ile Thr His Val Val Asn Ala Ala Ala Gly Lys Phe Gln Val
125 130 135
Asp Thr Gly Ala Lys Phe Tyr Arg Gly Met Ser Leu Glu Tyr Tyr
140 145 150
Gly Ile Glu Ala Asp Asp Asn Pro Phe Phe Asp Leu Ser Val Tyr
155 160 165
Phe Leu Pro Val Ala Arg Tyr Ile Arg Ala Ala Leu Ser Val Pro
170 175 180
Gln Gly Arg Val Leu Val His Cys Ala Met Gly Val Ser Arg Ser
185 190 195
Ala Thr Leu Val Leu Ala Phe Leu Met Ile Tyr Glu Asn Met Thr
200 205 210
Leu Val Glu Ala Ile Gln Thr Val Gln Ala His Arg Asn Ile Cys
215 220 225
Pro Asn Ser Gly Phe Leu Arg Gln Leu Gln Val Leu Asp Asn Arg
230 235 240
Leu Gly Arg Glu Thr Gly Arg Phe
245

<210> 12
<211> 810
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 1213802

<400> 12
Met Pro Asn Gln Gly Glu Asp Cys Tyr Phe Phe Phe Tyr Ser Thr
1 5 10 15
Cys Thr Lys Gly Asp Ser Cys Pro Phe Arg His Cys Glu Ala Ala
20 25 30
Ile Gly Asn Glu Thr Val Cys Thr Leu Trp Gln Glu Gly Arg Cys
35 40 45
Phe Arg Gln Val Cys Arg Phe Arg His Met Glu Ile Asp Lys Lys
50 55 60
Arg Ser Glu Ile Pro Cys Tyr Trp Glu Asn Gln Pro Thr Gly Cys
65 70 75
Gln Lys Leu Asn Cys Ala Phe His His Asn Arg Gly Arg Tyr Val
80 85 90
Asp Gly Leu Phe Leu Pro Pro Ser Lys Thr Val Leu Pro Thr Val
95 100 105
Pro Glu Ser Pro Glu Glu Glu Val Lys Ala Ser Gln Leu Ser Val
110 115 120
Gln Gln Asn Lys Leu Ser Val Gln Ser Asn Pro Ser Pro Gln Leu
125 130 135
Arg Ser Val Met Lys Val Glu Ser Ser Glu Asn Val Pro Ser Pro
140 145 150
Thr His Pro Pro Val Val Ile Asn Ala Ala Asp Asp Asp Glu Asp
155 160 165
Asp Asp Asp Gln Phe Ser Glu Glu Gly Asp Glu Thr Lys Thr Pro
170 175 180
Thr Leu Gln Pro Thr Pro Glu Val His Asn Gly Leu Arg Val Thr
185 190 195
Ser Val Arg Lys Pro Ala Val Asn Ile Lys Gln Gly Glu Cys Leu
200 205 210
Asn Phe Gly Ile Lys Thr Leu Glu Glu Ile Lys Ser Lys Lys Met
215 220 225
Lys Glu Lys Ser Lys Lys Gln Gly Glu Gly Ser Ser Gly Val Ser
230 235 240
Ser Leu Leu Leu His Pro Glu Pro Val Pro Gly Pro Glu Lys Glu
245 250 255
Asn Val Arg Thr Val Val Arg Thr Val Thr Leu Ser Thr Lys Gln
260 265 270
Gly Glu Glu Pro Leu Val Arg Leu Ser Leu Thr Glu Arg Leu Gly
275 280 285
Lys Arg Lys Phe Ser Ala Gly Gly Asp Ser Asp Pro Pro Leu Lys
290 295 300
Arg Ser Leu Ala Gln Arg Leu Gly Lys Lys Val Glu Ala Pro Glu
305 310 315
Thr Asn Ile Asp Lys Thr Pro Lys Lys Ala Gln Val Ser Lys Ser
320 325 330
Leu Lys Glu Arg Leu Gly Met Ser Ala Asp Pro Asp Asn Glu Asp
335 340 345
Ala Thr Asp Lys Val Asn Lys Val Gly Glu Ile His Val Lys Thr
350 355 360
Leu Glu Glu Ile Leu Leu Glu Arg Ala Ser Gln Lys Arg Gly Glu
365 370 375
Leu Gln Thr Lys Leu Lys Thr Glu Gly Pro Ser Lys Thr Asp Asp
380 385 390
Ser Thr Ser Gly Ala Arg Ser Ser Ser Thr Ile Arg Ile Lys Thr
395 400 405
Phe Ser Glu Val Leu Ala Glu Lys Lys His Arg Gln Gln Glu Ala

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                410                 415                 420
Glu Arg Gln Lys Ser Lys Lys Asp Thr Thr Cys Ile Lys Leu Lys
                425                 430                 435
Ile Asp Ser Glu Ile Lys Lys Thr Val Val Leu Pro Pro Ile Val
                440                 445                 450
Ala Ser Arg Gly Gln Ser Glu Glu Pro Ala Gly Lys Thr Lys Ser
                455                 460                 465
Met Gln Glu Val His Ile Lys Thr Leu Glu Glu Ile Lys Leu Glu
                470                 475                 480
Lys Ala Leu Arg Val Gln Gln Ser Ser Glu Ser Ser Thr Ser Ser
                485                 490                 495
Pro Ser Gln His Glu Ala Thr Pro Gly Ala Arg Arg Leu Leu Arg
                500                 505                 510
Ile Thr Lys Arg Thr Gly Met Lys Glu Glu Lys Asn Leu Gln Glu
                515                 520                 525
Gly Asn Glu Val Asp Ser Gln Ser Ser Ile Arg Thr Glu Ala Lys
                530                 535                 540
Glu Ala Ser Gly Glu Thr Thr Gly Val Asp Ile Thr Lys Ile Gln
                545                 550                 555
Val Lys Arg Cys Glu Thr Met Arg Glu Lys His Met Gln Lys Gln
                560                 565                 570
Gln Glu Arg Glu Lys Ser Val Leu Thr Pro Leu Arg Gly Asp Val
                575                 580                 585
Ala Ser Cys Asn Thr Gln Val Ala Glu Lys Pro Val Leu Thr Ala
                590                 595                 600
Val Pro Gly Ile Thr Arg His Leu Thr Lys Arg Leu Pro Thr Lys
                605                 610                 615
Ser Ser Gln Lys Val Glu Val Glu Thr Ser Gly Ile Gly Asp Ser
                620                 625                 630
Leu Leu Asn Val Lys Cys Ala Ala Gln Thr Leu Glu Lys Arg Gly
                635                 640                 645
Lys Ala Lys Pro Lys Val Asn Val Lys Pro Ser Val Val Lys Val
                650                 655                 660
Val Ser Ser Pro Lys Leu Ala Pro Lys Arg Lys Ala Val Glu Met
                665                 670                 675
His Ala Ala Val Ile Ala Ala Val Lys Pro Leu Ser Ser Ser Ser
                680                 685                 690
Val Leu Gln Glu Pro Pro Ala Lys Lys Ala Ala Val Ala Val Val
                695                 700                 705
Pro Leu Val Ser Glu Asp Lys Ser Val Thr Val Pro Glu Ala Glu
                710                 715                 720
Asn Pro Arg Asp Ser Leu Val Leu Pro Pro Thr Gln Ser Ser Ser
                725                 730                 735
Asp Ser Ser Pro Pro Glu Val Ser Gly Pro Ser Ser Ser Gln Met
                740                 745                 750
Ser Met Lys Thr Arg Arg Leu Ser Ser Ala Ser Thr Gly Lys Pro
                755                 760                 765
Pro Leu Ser Val Glu Asp Asp Phe Glu Lys Leu Ile Trp Glu Ile
                770                 775                 780
Ser Gly Gly Lys Leu Glu Ala Glu Ile Asp Leu Asp Pro Gly Lys
                785                 790                 795
Asp Glu Asp Asp Leu Leu Leu Glu Leu Ser Glu Met Ile Asp Ser
                800                 805                 810
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<210> 13

<211> 549
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 1378134

<400> 13
Met Arg Arg Arg Ala Ser Asn Ala Ala Ala Ala Ala His Thr Ile
1 5 10 15
Gly Gly Ser Lys His Thr Met Asn Asp His Leu His Val Gly Ser
20 25 30
His Ala His Gly Gln Ile Gln Val Arg Gln Leu Phe Glu Asp Asn
35 40 45
Ser Asn Lys Arg Thr Val Leu Thr Thr Gln Pro Asn Gly Leu Thr
50 55 60
Thr Val Gly Lys Thr Gly Leu Pro Val Val Pro Glu Arg Gln Leu
65 70 75
Asp Ser Ile His Arg Arg Gln Gly Ser Ser Thr Ser Leu Lys Ser
80 85 90
Met Glu Gly Met Gly Lys Val Lys Ala Thr Pro Met Thr Pro Glu
95 100 105
Gln Ala Met Lys Gln Tyr Met Gln Lys Leu Thr Ala Phe Glu His
110 115 120
His Glu Ile Phe Ser Tyr Pro Glu Ile Tyr Phe Leu Gly Leu Asn
125 130 135
Ala Lys Lys Arg Gln Gly Met Thr Gly Gly Pro Asn Asn Gly Gly
140 145 150
Tyr Asp Asp Asp Gln Gly Ser Tyr Val Gln Val Pro His Asp His
155 160 165
Val Ala Tyr Arg Tyr Glu Val Leu Lys Val Ile Gly Lys Gly Ser
170 175 180
Phe Gly Gln Val Val Lys Ala Tyr Asp His Lys Val His Gln His
185 190 195
Val Ala Leu Lys Met Val Arg Asn Glu Lys Arg Phe His Arg Gln
200 205 210
Ala Ala Glu Glu Ile Arg Ile Leu Glu His Leu Arg Lys Gln Asp
215 220 225
Lys Asp Asn Thr Met Asn Val Ile His Met Leu Glu Asn Phe Thr
230 235 240
Phe Arg Asn His Ile Cys Met Thr Phe Glu Leu Leu Ser Met Asn
245 250 255
Leu Tyr Glu Leu Ile Lys Lys Asn Lys Phe Gln Gly Phe Ser Leu
260 265 270
Pro Leu Val Arg Lys Phe Ala His Ser Ile Leu Gln Cys Leu Asp
275 280 285
Ala Leu His Lys Asn Arg Ile Ile His Cys Asp Leu Lys Pro Glu
290 295 300
Asn Ile Leu Leu Lys Gln Gln Gly Arg Ser Gly Ile Lys Val Ile
305 310 315
Asp Phe Gly Ser Ser Cys Tyr Glu His Gln Arg Val Tyr Thr Tyr
320 325 330
Ile Gln Ser Arg Phe Tyr Arg Ala Pro Glu Val Ile Leu Gly Ala
335 340 345
Arg Tyr Gly Met Pro Ile Asp Met Trp Ser Leu Gly Cys Ile Leu

```
                    350                 355                 360
Ala Glu Leu Leu Thr Gly Tyr Pro Leu Leu Pro Gly Glu Asp Glu
                365                 370                 375
Gly Asp Gln Leu Ala Cys Met Ile Glu Leu Leu Gly Met Pro Ser
                380                 385                 390
Gln Lys Leu Leu Asp Ala Ser Lys Arg Ala Lys Asn Phe Val Ser
                395                 400                 405
Ser Lys Gly Tyr Pro Arg Tyr Cys Thr Val Thr Thr Leu Ser Asp
                410                 415                 420
Gly Ser Val Val Leu Asn Gly Gly Arg Ser Arg Arg Gly Lys Leu
                425                 430                 435
Arg Gly Pro Pro Glu Ser Arg Glu Trp Gly Asn Ala Leu Lys Gly
                440                 445                 450
Cys Asp Asp Pro Leu Phe Leu Asp Phe Leu Lys Gln Cys Leu Glu
                455                 460                 465
Trp Asp Pro Ala Val Arg Met Thr Pro Gly Gln Ala Leu Arg His
                470                 475                 480
Pro Trp Leu Arg Arg Arg Leu Pro Lys Pro Pro Thr Gly Glu Lys
                485                 490                 495
Thr Ser Val Lys Arg Ile Thr Glu Ser Thr Gly Ala Ile Thr Ser
                500                 505                 510
Ile Ser Lys Leu Pro Pro Pro Ser Ser Ser Ala Ser Lys Leu Arg
                515                 520                 525
Thr Asn Leu Ala Gln Met Thr Asp Ala Asn Gly Asn Ile Gln Gln
                530                 535                 540
Arg Thr Val Leu Pro Lys Leu Val Ser
                545
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<210> 14
<211> 416
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 1490070

<400> 14

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Met Met Pro Gln Leu Gln Phe Lys Asp Ala Phe Trp Cys Arg Asp
 1               5                  10                  15
Phe Thr Ala His Thr Gly Tyr Glu Val Leu Leu Gln Arg Leu Leu
                20                  25                  30
Asp Gly Arg Lys Met Cys Lys Asp Met Val Glu Leu Leu Trp Gln
                35                  40                  45
Arg Ala Gln Ala Glu Glu Arg Tyr Gly Lys Glu Leu Val Gln Ile
                50                  55                  60
Ala Arg Lys Ala Gly Gly Gln Thr Glu Ile Asn Ser Leu Arg Ala
                65                  70                  75
Ser Phe Asp Ser Leu Lys Gln Gln Met Glu Asn Val Gly Ser Ser
                80                  85                  90
His Ile Gln Leu Ala Leu Thr Leu Arg Glu Glu Leu Arg Ser Leu
                95                  100                 105
Glu Glu Phe Arg Glu Arg Gln Lys Glu Gln Arg Lys Lys Tyr Glu
                110                 115                 120
Ala Val Met Asp Arg Val Gln Lys Ser Lys Leu Ser Leu Tyr Lys
```

```
                125                 130                 135
Lys Ala Met Glu Ser Lys Lys Thr Tyr Glu Gln Lys Cys Arg Asp
                140                 145                 150
Ala Asp Asp Ala Glu Gln Ala Phe Glu Arg Ile Ser Ala Asn Gly
                155                 160                 165
His Gln Lys Gln Val Glu Lys Ser Gln Asn Lys Ala Arg Gln Cys
                170                 175                 180
Lys Asp Ser Ala Thr Glu Ala Glu Arg Val Tyr Arg Gln Ser Ile
                185                 190                 195
Ala Gln Leu Glu Lys Val Arg Ala Glu Trp Glu Gln Glu His Arg
                200                 205                 210
Thr Thr Cys Glu Ala Phe Gln Leu Gln Glu Phe Asp Arg Leu Thr
                215                 220                 225
Ile Leu Arg Asn Ala Leu Trp Val His Ser Asn Gln Leu Ser Met
                230                 235                 240
Gln Cys Val Lys Asp Asp Glu Leu Tyr Glu Glu Val Arg Leu Thr
                245                 250                 255
Leu Glu Gly Cys Ser Ile Asp Ala Asp Ile Asp Ser Phe Ile Gln
                260                 265                 270
Ala Lys Ser Thr Gly Thr Glu Pro Pro Ala Pro Val Pro Tyr Gln
                275                 280                 285
Asn Tyr Tyr Asp Arg Glu Val Thr Pro Leu Thr Ser Ser Pro Gly
                290                 295                 300
Ile Gln Pro Ser Cys Gly Met Ile Lys Arg Phe Ser Gly Leu Leu
                305                 310                 315
His Gly Ser Pro Lys Thr Thr Ser Leu Ala Ala Ser Ala Ala Ser
                320                 325                 330
Thr Glu Thr Leu Thr Pro Thr Pro Glu Arg Asn Glu Gly Val Tyr
                335                 340                 345
Thr Ala Ile Ala Val Gln Glu Ile Gln Gly Asn Pro Ala Ser Pro
                350                 355                 360
Ala Gln Glu Tyr Arg Ala Leu Tyr Asp Tyr Thr Ala Gln Asn Pro
                365                 370                 375
Asp Glu Leu Asp Leu Ser Ala Gly Asp Ile Leu Glu Val Ile Leu
                380                 385                 390
Glu Gly Glu Asp Gly Trp Trp Thr Val Glu Arg Asn Gly Gln Arg
                395                 400                 405
Gly Phe Val Pro Gly Ser Tyr Leu Glu Lys Leu
                410                 415
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<210> 15
<211> 425
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 1997814

<400> 15

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Met Glu Gln Gly Leu Glu Glu Glu Glu Glu Val Asp Pro Arg Ile
  1               5                  10                  15
Gln Gly Glu Leu Glu Lys Leu Asn Gln Ser Thr Asp Asp Ile Asn
                 20                  25                  30
Arg Arg Glu Thr Glu Leu Glu Asp Ala Arg Gln Lys Phe Arg Ser
                 35                  40                  45
```

Val Leu Val Glu Ala Thr Val Lys Leu Asp Glu Leu Val Lys Lys
50 55 60
Ile Gly Lys Ala Val Glu Asp Ser Lys Pro Tyr Trp Glu Ala Arg
65 70 75
Arg Val Ala Arg Gln Ala Gln Leu Glu Ala Gln Lys Ala Thr Gln
80 85 90
Asp Phe Gln Arg Ala Thr Glu Val Leu Arg Ala Ala Lys Glu Thr
95 100 105
Ile Ser Leu Ala Glu Gln Arg Leu Leu Glu Asp Asp Lys Arg Gln
110 115 120
Phe Asp Ser Ala Trp Gln Glu Met Leu Asn His Ala Thr Gln Arg
125 130 135
Val Met Glu Ala Glu Gln Thr Lys Thr Arg Ser Glu Leu Val His
140 145 150
Lys Glu Thr Ala Ala Arg Tyr Asn Ala Ala Met Gly Arg Met Arg
155 160 165
Gln Leu Glu Lys Lys Leu Lys Arg Ala Ile Asn Lys Ser Lys Pro
170 175 180
Tyr Phe Glu Leu Lys Ala Lys Tyr Tyr Val Gln Leu Glu Gln Leu
185 190 195
Lys Lys Thr Val Asp Asp Leu Gln Ala Lys Leu Thr Leu Ala Lys
200 205 210
Gly Glu Tyr Lys Met Ala Leu Lys Asn Leu Glu Met Ile Ser Asp
215 220 225
Glu Ile His Glu Arg Arg Arg Ser Ser Ala Met Gly Pro Arg Gly
230 235 240
Cys Gly Val Gly Ala Glu Gly Ser Ser Thr Ser Val Glu Asp Leu
245 250 255
Pro Gly Ser Lys Pro Glu Pro Asp Ala Ile Ser Val Ala Ser Glu
260 265 270
Ala Phe Glu Asp Asp Ser Cys Ser Asn Phe Val Ser Glu Asp Asp
275 280 285
Ser Glu Thr Gln Ser Val Ser Ser Phe Ser Ser Gly Pro Thr Ser
290 295 300
Pro Ser Glu Met Pro Asp Gln Phe Pro Ala Val Val Arg Pro Gly
305 310 315
Ser Leu Asp Leu Pro Ser Pro Val Ser Leu Ser Glu Phe Gly Met
320 325 330
Met Phe Pro Val Leu Gly Pro Arg Ser Glu Cys Ser Gly Ala Ser
335 340 345
Ser Pro Glu Cys Glu Val Glu Arg Gly Asp Arg Ala Glu Gly Ala
350 355 360
Glu Asn Lys Thr Ser Asp Lys Ala Asn Asn Asn Arg Gly Leu Ser
365 370 375
Ser Ser Ser Gly Ser Gly Gly Ser Ser Lys Ser Gln Ser Ser Thr
380 385 390
Ser Pro Glu Gly Gln Ala Leu Glu Asn Arg Met Lys Gln Leu Ser
395 400 405
Leu Gln Cys Ser Lys Gly Arg Asp Gly Ile Ile Ala Asp Ile Lys
410 415 420
Met Val Gln Ile Gly
425

<210> 16
<211> 1135

<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 2299715

<400> 16
Met Ala Asn Asp Ser Pro Ala Lys Ser Leu Val Asp Ile Asp Leu
1 5 10 15
Ser Ser Leu Arg Asp Pro Ala Gly Ile Phe Glu Leu Val Glu Val
20 25 30
Val Gly Asn Gly Thr Tyr Gly Gln Val Tyr Lys Gly Arg His Val
35 40 45
Lys Thr Gly Gln Leu Ala Ala Ile Lys Val Met Asp Val Thr Glu
50 55 60

Asp Glu Glu Glu Glu Ile Lys Leu Glu Ile Asn Met Leu Lys Lys
65 70 75
Tyr Ser His His Arg Asn Ile Ala Thr Tyr Tyr Gly Ala Phe Ile
80 85 90
Lys Lys Ser Pro Pro Gly His Asp Asp Gln Leu Trp Leu Val Met
95 100 105
Glu Phe Cys Gly Ala Gly Ser Ile Thr Asp Leu Val Lys Asn Thr
110 115 120
Lys Gly Asn Thr Leu Lys Glu Asp Trp Ile Ala Tyr Ile Ser Arg
125 130 135
Glu Ile Leu Arg Gly Leu Ala His Leu His Ile His His Val Ile
140 145 150
His Arg Asp Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala
155 160 165
Gly Val Lys Leu Val Asp Phe Gly Val Ser Ala Gln Leu Asp Arg
170 175 180
Thr Val Gly Arg Arg Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met
185 190 195
Ala Pro Glu Val Ile Ala Cys Asp Glu Asn Pro Asp Ala Thr Tyr
200 205 210
Asp Tyr Arg Ser Asp Leu Trp Ser Cys Gly Ile Thr Ala Ile Glu
215 220 225
Met Ala Glu Gly Ala Pro Pro Leu Cys Asp Met His Pro Met Arg
230 235 240
Ala Leu Phe Leu Ile Pro Arg Asn Pro Pro Pro Arg Leu Lys Ser
245 250 255
Lys Lys Trp Ser Lys Lys Phe Phe Ser Phe Ile Glu Gly Cys Leu
260 265 270
Val Lys Asn Tyr Met Gln Arg Pro Ser Thr Glu Gln Leu Leu Lys
275 280 285
His Pro Phe Ile Arg Asp Gln Pro Asn Glu Arg Gln Val Arg Ile
290 295 300
Gln Leu Lys Asp His Ile Asp Arg Thr Arg Lys Lys Arg Gly Glu
305 310 315
Lys Asp Glu Thr Glu Tyr Glu Tyr Ser Gly Ser Glu Glu Glu Glu
320 325 330
Glu Glu Val Pro Glu Gln Glu Gly Glu Pro Ser Ser Ile Val Asn
335 340 345
Val Pro Gly Glu Ser Thr Leu Arg Arg Asp Phe Leu Arg Leu Gln

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                350                 355                 360
Gln Glu Asn Lys Glu Arg Ser Glu Ala Leu Arg Arg Gln Gln Leu
                365                 370                 375
Leu Gln Glu Gln Gln Leu Arg Glu Gln Glu Glu Tyr Lys Arg Gln
                380                 385                 390
Leu Leu Ala Glu Arg Gln Lys Arg Ile Glu Gln Gln Lys Glu Gln
                395                 400                 405
Arg Arg Arg Leu Glu Glu Gln Gln Arg Arg Glu Arg Glu Ala Arg
                410                 415                 420
Arg Gln Gln Glu Arg Glu Gln Arg Arg Arg Glu Gln Glu Glu Lys
                425                 430                 435
Arg Arg Leu Glu Glu Leu Glu Arg Arg Arg Lys Glu Glu Glu Glu
                440                 445                 450
Arg Arg Arg Ala Glu Glu Glu Lys Arg Arg Val Glu Arg Glu Gln
                455                 460                 465
Glu Tyr Ile Arg Arg Gln Leu Glu Glu Glu Gln Arg His Leu Glu
                470                 475                 480
Val Leu Gln Gln Gln Leu Leu Gln Glu Gln Ala Met Leu Leu His
                485                 490                 495
Asp His Arg Arg Pro His Pro Gln His Ser Gln Gln Pro Pro Pro
                500                 505                 510
Pro Gln Gln Glu Arg Ser Lys Pro Ser Phe His Ala Pro Glu Pro
                515                 520                 525
Lys Ala His Tyr Glu Pro Ala Asp Arg Ala Arg Glu Val Pro Val
                530                 535                 540
Arg Thr Thr Ser Arg Ser Pro Val Leu Ser Arg Arg Asp Ser Pro
                545                 550                 555
Leu Gln Gly Ser Gly Gln Gln Asn Ser Gln Ala Gly Gln Arg Asn
                560                 565                 570
Ser Thr Ser Ile Glu Pro Arg Leu Leu Trp Glu Arg Val Glu Lys
                575                 580                 585
Leu Val Pro Arg Pro Gly Ser Gly Ser Ser Ser Gly Ser Ser Asn
                590                 595                 600
Ser Gly Ser Gln Pro Gly Ser His Pro Gly Ser Gln Ser Gly Ser
                605                 610                 615
Gly Glu Arg Phe Arg Val Arg Ser Ser Ser Lys Ser Glu Gly Ser
                620                 625                 630
Pro Ser Gln Arg Leu Glu Asn Ala Val Lys Lys Pro Glu Asp Lys
                635                 640                 645
Lys Glu Val Phe Arg Pro Leu Lys Pro Ala Asp Leu Thr Ala Leu
                650                 655                 660
Ala Lys Glu Leu Arg Ala Val Glu Asp Val Arg Pro Pro His Lys
                665                 670                 675
Val Thr Asp Tyr Ser Ser Ser Ser Glu Glu Ser Gly Thr Thr Asp
                680                 685                 690
Glu Glu Asp Asp Asp Val Glu Gln Glu Gly Ala Asp Glu Ser Thr
                695                 700                 705
Ser Gly Pro Glu Asp Thr Arg Ala Ala Ser Ser Leu Asn Leu Ser
                710                 715                 720
Asn Gly Glu Thr Glu Ser Val Lys Thr Met Ile Val His Asp Asp
                725                 730                 735
Val Glu Ser Glu Pro Ala Met Thr Pro Ser Lys Glu Gly Thr Leu
                740                 745                 750
Ile Val Arg Gln Thr Gln Ser Ala Ser Ser Thr Leu Gln Lys His
                755                 760                 765
Lys Ser Ser Ser Ser Phe Thr Pro Phe Ile Asp Pro Arg Leu Leu
```

770 775 780
Gln Ile Ser Pro Ser Ser Gly Thr Thr Val Thr Ser Val Val Gly
785 790 795
Phe Ser Cys Asp Gly Met Arg Pro Glu Ala Ile Arg Gln Asp Pro
800 805 810
Thr Arg Lys Gly Ser Val Val Asn Val Asn Pro Thr Asn Thr Arg
815 820 825
Pro Gln Ser Asp Thr Pro Glu Ile Arg Lys Tyr Lys Lys Arg Phe
830 835 840
Asn Ser Glu Ile Leu Cys Ala Ala Leu Trp Gly Val Asn Leu Leu
845 850 855
Val Gly Thr Glu Ser Gly Leu Met Leu Leu Asp Arg Ser Gly Gln
860 865 870
Gly Lys Val Tyr Pro Leu Ile Asn Arg Arg Arg Phe Gln Gln Met
875 880 885
Asp Val Leu Glu Gly Leu Asn Val Leu Val Thr Ile Ser Gly Lys
890 895 900
Lys Asp Lys Leu Arg Val Tyr Tyr Leu Ser Trp Leu Arg Asn Lys
905 910 915
Ile Leu His Asn Asp Pro Glu Val Glu Lys Lys Gln Gly Trp Thr
920 925 930
Thr Val Gly Asp Leu Glu Gly Cys Val His Tyr Lys Val Val Lys
935 940 945
Tyr Glu Arg Ile Lys Phe Leu Val Ile Ala Leu Lys Ser Ser Val
950 955 960
Glu Val Tyr Ala Trp Ala Pro Lys Pro Tyr His Lys Phe Met Ala
965 970 975
Phe Lys Ser Phe Gly Glu Leu Val His Gly Ser Cys Ala Gly Phe
980 985 990
His Ala Val Asp Val Asp Ser Gly Ser Val Tyr Asp Ile Tyr Leu
995 1000 1005
Pro Thr His Ile Gln Cys Ser Ile Lys Pro His Ala Ile Ile Ile
1010 1015 1020
Leu Pro Asn Thr Asp Gly Met Glu Leu Leu Val Cys Tyr Glu Asp
1025 1030 1035
Glu Gly Val Tyr Val Asn Thr Tyr Gly Arg Ile Thr Lys Asp Val
1040 1045 1050
Val Leu Gln Trp Gly Glu Met Pro Thr Ser Val Ala Tyr Ile Arg
1055 1060 1065
Ser Asn Gln Thr Met Gly Trp Gly Glu Lys Ala Ile Glu Ile Arg
1070 1075 1080
Ser Val Glu Thr Gly His Leu Asp Gly Val Phe Met His Lys Arg
1085 1090 1095
Ala Gln Arg Leu Lys Phe Leu Cys Glu Arg Asn Asp Lys Val Phe
1100 1105 1110
Phe Ala Ser Val Arg Ser Gly Gly Ser Ser Gln Val Tyr Phe Met
1115 1120 1125
Thr Leu Gly Arg Thr Ser Leu Leu Ser Trp
1130 1135

<210> 17
<211> 228
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 209854

<400> 17
Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn
1 5 10 15
Lys His Ile Asn Ile Ser Phe His Arg Phe Pro Leu Asp Pro Lys
20 25 30
Arg Arg Lys Glu Trp Val Arg Leu Val Arg Arg Lys Asn Phe Val
35 40 45
Pro Gly Lys His Thr Phe Leu Cys Ser Lys His Phe Glu Ala Ser
50 55 60
Cys Phe Asp Leu Thr Gly Gln Thr Arg Arg Leu Lys Met Asp Ala
65 70 75
Val Pro Thr Ile Phe Asp Phe Cys Thr His Ile Lys Ser Met Lys
80 85 90
Leu Lys Ser Arg Asn Leu Leu Lys Lys Asn Asn Ser Cys Ser Pro
95 100 105
Ala Gly Pro Ser Asn Leu Lys Ser Asn Ile Ser Ser Gln Gln Val
110 115 120
Leu Leu Glu His Ser Tyr Ala Phe Arg Asn Pro Met Glu Ala Lys
125 130 135
Lys Arg Ile Ile Lys Leu Glu Lys Glu Ile Ala Ser Leu Arg Arg
140 145 150
Lys Met Lys Thr Cys Leu Gln Lys Glu Arg Arg Ala Thr Arg Arg
155 160 165
Trp Ile Lys Ala Thr Cys Leu Val Lys Asn Leu Glu Ala Asn Ser
170 175 180
Val Leu Pro Lys Gly Thr Ser Glu His Met Leu Pro Thr Ala Leu
185 190 195
Ser Ser Leu Pro Leu Glu Asp Phe Lys Ile Leu Glu Gln Asp Gln
200 205 210
Gln Asp Lys Thr Leu Leu Ser Leu Asn Leu Lys Gln Thr Lys Ser
215 220 225
Thr Phe Ile

<210> 18
<211> 503
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 1384286

<400> 18
Met Ala Thr Thr Val Thr Cys Thr Arg Phe Thr Asp Glu Tyr Gln
1 5 10 15
Leu Tyr Glu Asp Ile Gly Lys Gly Ala Phe Ser Val Val Arg Arg
20 25 30
Cys Val Lys Leu Cys Thr Gly His Glu Tyr Ala Ala Lys Ile Ile
35 40 45
Asn Thr Lys Lys Leu Ser Ala Arg Asp His Gln Lys Leu Glu Arg

50 55 60
Glu Ala Arg Ile Cys Arg Leu Leu Lys His Ser Asn Ile Val Arg
65 70 75
Leu His Asp Ser Ile Ser Glu Glu Gly Phe His Tyr Leu Val Phe
80 85 90
Asp Leu Val Thr Gly Gly Glu Leu Phe Glu Asp Ile Val Ala Arg
95 100 105
Glu Tyr Tyr Ser Glu Ala Asp Ala Ser His Cys Ile Gln Gln Ile
110 115 120
Leu Glu Ala Val Leu His Cys His Gln Met Gly Val Val His Arg
125 130 135
Asp Leu Lys Pro Glu Asn Leu Leu Leu Ala Ser Lys Cys Lys Gly
140 145 150
Ala Ala Val Lys Leu Ala Asp Phe Gly Leu Ala Ile Glu Val Gln
155 160 165
Gly Asp Gln Gln Ala Trp Phe Gly Phe Ala Gly Thr Pro Gly Tyr
170 175 180
Leu Ser Pro Glu Val Leu Arg Lys Glu Ala Tyr Gly Lys Pro Val
185 190 195
Asp Ile Trp Ala Cys Gly Val Ile Leu Tyr Ile Leu Leu Val Gly
200 205 210
Tyr Pro Pro Phe Trp Asp Glu Asp Gln His Lys Leu Tyr Gln Gln
215 220 225
Ile Lys Ala Gly Ala Tyr Asp Phe Pro Ser Pro Glu Trp Asp Thr
230 235 240
Val Thr Pro Glu Ala Lys Asn Leu Ile Asn Gln Met Leu Thr Ile
245 250 255
Asn Pro Ala Lys Arg Ile Thr Ala His Glu Ala Leu Lys His Pro
260 265 270
Trp Val Cys Gln Arg Ser Thr Val Ala Ser Met Met His Arg Gln
275 280 285
Glu Thr Val Glu Cys Leu Lys Lys Phe Asn Ala Arg Arg Lys Leu
290 295 300
Lys Gly Ala Ile Leu Thr Thr Met Leu Ala Thr Arg Asn Phe Ser
305 310 315
Ala Ala Lys Ser Leu Leu Asn Lys Lys Ala Asp Gly Val Lys Pro
320 325 330
His Thr Asn Ser Thr Lys Asn Ser Ala Ala Ala Thr Ser Pro Lys
335 340 345
Gly Thr Leu Pro Pro Ala Ala Leu Glu Ser Ser Asp Ser Ala Asn
350 355 360
Thr Thr Ile Glu Asp Glu Asp Ala Lys Ala Arg Lys Gln Glu Ile
365 370 375
Ile Lys Thr Thr Glu Gln Leu Ile Glu Ala Val Asn Asn Gly Asp
380 385 390
Phe Glu Ala Tyr Ala Lys Ile Cys Asp Pro Gly Leu Thr Ser Phe
395 400 405
Glu Pro Glu Ala Leu Gly Asn Leu Val Glu Gly Met Asp Phe His
410 415 420
Arg Phe Tyr Phe Glu Asn Leu Leu Ala Lys Asn Ser Lys Pro Ile
425 430 435
His Thr Thr Ile Leu Asn Pro His Val His Val Ile Gly Glu Asp
440 445 450
Ala Ala Cys Ile Ala Tyr Ile Arg Leu Thr Gln Tyr Ile Asp Gly
455 460 465
Gln Gly Arg Pro Arg Thr Ser Gln Ser Glu Glu Thr Arg Val Trp

```
                470                 475                 480
His Arg Arg Asp Gly Lys Trp Gln Asn Val His Phe His Cys Ser
                485                 490                 495
Gly Ala Pro Val Ala Pro Leu Gln
                500
```

<210> 19
<211> 433
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 1512656

<400> 19

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Met Thr Gly Glu Ala Gln Ala Gly Arg Lys Arg Ser Arg Ala Arg
 1               5                  10                  15
Pro Glu Gly Thr Glu Pro Val Arg Arg Glu Arg Thr Gln Pro Gly
                20                  25                  30
Leu Gly Pro Gly Arg Ala Arg Ala Met Ala Ala Glu Ala Thr Ala
                35                  40                  45
Val Ala Gly Ser Gly Ala Val Gly Gly Cys Leu Ala Lys Asp Gly
                50                  55                  60
Leu Gln Gln Ser Lys Cys Pro Asp Thr Thr Pro Lys Arg Arg Arg
                65                  70                  75
Ala Ser Ser Leu Ser Arg Asp Ala Glu Arg Arg Ala Tyr Gln Trp
                80                  85                  90
Cys Arg Glu Tyr Leu Gly Gly Ala Trp Arg Arg Val Gln Pro Glu
                95                 100                 105
Glu Leu Arg Val Tyr Pro Val Ser Gly Gly Leu Ser Asn Leu Leu
               110                 115                 120
Phe Arg Cys Ser Leu Pro Asp His Leu Pro Ser Val Gly Glu Glu
               125                 130                 135
Pro Arg Glu Val Leu Leu Arg Leu Tyr Gly Ala Ile Leu Gln Gly
               140                 145                 150
Val Asp Ser Leu Val Leu Glu Ser Val Met Phe Ala Ile Leu Ala
               155                 160                 165
Glu Arg Ser Leu Gly Pro Gln Leu Tyr Gly Val Phe Pro Glu Gly
               170                 175                 180
Arg Leu Glu Gln Tyr Ile Pro Ser Arg Pro Leu Lys Thr Gln Glu
               185                 190                 195
Leu Arg Glu Pro Val Leu Ser Ala Ala Ile Ala Thr Lys Met Ala
               200                 205                 210
Gln Phe His Gly Met Glu Met Pro Phe Thr Lys Glu Pro His Trp
               215                 220                 225
Leu Phe Gly Thr Met Glu Arg Tyr Leu Lys Gln Ile Gln Asp Leu
               230                 235                 240
Pro Pro Thr Gly Leu Pro Glu Met Asn Leu Leu Glu Met Tyr Ser
               245                 250                 255
Leu Lys Asp Glu Met Gly Asn Leu Arg Lys Leu Leu Glu Ser Thr
               260                 265                 270
Pro Ser Pro Val Val Phe Cys His Asn Asp Ile Gln Glu Gly Asn
```

```
                275                 280                 285
Ile Leu Leu Leu Ser Glu Pro Glu Asn Ala Asp Ser Leu Met Leu
                290                 295                 300
Val Asp Phe Glu Tyr Ser Ser Tyr Asn Tyr Arg Gly Phe Asp Ile
                305                 310                 315
Gly Asn His Phe Cys Glu Trp Val Tyr Asp Tyr Thr His Glu Glu
                320                 325                 330
Trp Pro Phe Tyr Lys Ala Arg Pro Thr Asp Tyr Pro Thr Gln Glu
                335                 340                 345
Gln Gln Leu His Phe Ile Arg His Tyr Leu Ala Glu Ala Lys Lys
                350                 355                 360
Gly Glu Thr Leu Ser Gln Glu Glu Gln Arg Lys Leu Glu Glu Asp
                365                 370                 375
Leu Leu Val Glu Val Ser Arg Tyr Ala Leu Ala Ser His Phe Phe
                380                 385                 390
Trp Gly Leu Trp Ser Ile Leu Gln Ala Ser Met Ser Thr Ile Glu
                395                 400                 405
Phe Gly Tyr Leu Asp Tyr Ala Gln Ser Arg Phe Gln Phe Tyr Phe
                410                 415                 420
Gln Gln Lys Gly Gln Leu Thr Ser Val His Ser Ser Ser
                425                 430


<210> 20
<211> 527
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 2098635

<400> 20
Met Ser Leu Cys Gly Ala Arg Ala Asn Ala Lys Met Met Ala Ala
  1               5                  10                  15
Tyr Asn Gly Gly Thr Ser Ala Ala Ala Ala Gly His His His His
                 20                  25                  30
His His His His Leu Pro His Leu Pro Pro Pro His Leu Leu His
                 35                  40                  45
His His His Pro Gln His His Leu His Pro Gly Ser Ala Ala Ala
                 50                  55                  60
Val His Pro Val Gln Gln His Thr Ser Ser Ala Ala Ala Ala Ala
                 65                  70                  75
Ala Ala Ala Ala Ala Ala Ala Ala Met Leu Asn Pro Gly Gln Gln
                 80                  85                  90
Gln Pro Tyr Phe Pro Ser Pro Ala Pro Gly Gln Ala Pro Gly Pro
                 95                 100                 105
Ala Ala Ala Ala Pro Ala Gln Val Gln Ala Ala Ala Ala Ala Thr
                110                 115                 120
Val Lys Ala His His His Gln His Ser His His Pro Gln Gln Gln
                125                 130                 135
Leu Asp Ile Glu Pro Asp Arg Pro Ile Gly Tyr Gly Ala Phe Gly
                140                 145                 150
Val Val Trp Ser Val Thr Asp Pro Arg Asp Gly Lys Arg Val Ala
                155                 160                 165
Leu Lys Lys Met Pro Asn Val Phe Gln Asn Leu Val Ser Cys Lys
```

```
                170                 175                 180
Arg Val Phe Arg Glu Leu Lys Met Leu Cys Phe Phe Lys His Asp
                185                 190                 195
Asn Val Leu Ser Ala Leu Asp Ile Leu Gln Pro Pro His Ile Asp
                200                 205                 210
Tyr Phe Glu Glu Ile Tyr Val Val Thr Glu Leu Met Gln Ser Asp
                215                 220                 225
Leu His Lys Ile Ile Val Ser Pro Gln Pro Leu Ser Ser Asp His
                230                 235                 240
Val Lys Val Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Leu
                245                 250                 255
His Ser Ala Gly Ile Leu His Arg Asp Ile Lys Pro Gly Asn Leu
                260                 265                 270
Leu Val Asn Ser Asn Cys Val Leu Lys Ile Cys Asp Phe Gly Leu
                275                 280                 285
Ala Arg Val Glu Glu Leu Asp Glu Ser Arg His Met Thr Gln Glu
                290                 295                 300
Val Val Thr Gln Tyr Tyr Arg Ala Pro Glu Ile Leu Met Gly Ser
                305                 310                 315
Arg His Tyr Ser Asn Ala Ile Asp Ile Trp Ser Val Gly Cys Ile
                320                 325                 330
Phe Ala Glu Leu Leu Gly Arg Arg Ile Leu Phe Gln Ala Gln Ser
                335                 340                 345
Pro Ile Gln Gln Leu Asp Leu Ile Thr Asp Leu Leu Gly Thr Pro
                350                 355                 360
Ser Leu Glu Ala Met Arg Thr Ala Cys Glu Gly Ala Lys Ala His
                365                 370                 375
Ile Leu Arg Gly Pro His Lys Gln Pro Ser Leu Pro Val Leu Tyr
                380                 385                 390
Thr Leu Ser Ser Gln Ala Thr His Glu Ala Val His Leu Leu Cys
                395                 400                 405
Arg Met Leu Val Phe Asp Pro Ser Lys Arg Ile Ser Ala Lys Asp
                410                 415                 420
Ala Leu Ala His Pro Tyr Leu Asp Glu Gly Arg Leu Arg Tyr His
                425                 430                 435
Thr Cys Met Cys Lys Cys Cys Phe Ser Thr Ser Thr Gly Arg Val
                440                 445                 450
Tyr Thr Ser Asp Phe Glu Pro Val Thr Asn Pro Lys Phe Asp Asp
                455                 460                 465
Thr Phe Glu Lys Asn Leu Ser Ser Val Arg Gln Val Lys Glu Ile
                470                 475                 480
Ile His Gln Phe Ile Leu Glu Gln Gln Lys Gly Asn Arg Val Pro
                485                 490                 495
Leu Cys Ile Asn Pro Gln Ser Ala Ala Phe Lys Ser Phe Ile Ser
                500                 505                 510
Ser Thr Val Ala Gln Pro Ser Glu Met Pro Pro Ser Pro Leu Val
                515                 520                 525
Trp Glu
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<210> 21
<211> 322
<212> PRT
<213> Homo sapiens

<220>

<221> misc_feature
<223> Incyte Clone Number: 2446646

<400> 21
Met Glu Gly Ile Ser Asn Phe Lys Thr Pro Ser Lys Leu Ser Glu
1 5 10 15
Lys Lys Lys Ser Val Leu Cys Ser Thr Pro Thr Ile Asn Ile Pro
20 25 30
Ala Ser Pro Phe Met Gln Lys Leu Gly Phe Gly Thr Gly Val Asn
35 40 45
Val Tyr Leu Met Lys Arg Ser Pro Arg Gly Leu Ser His Ser Pro
50 55 60
Trp Ala Val Lys Lys Ile Asn Pro Ile Cys Asn Asp His Tyr Arg
65 70 75
Ser Val Tyr Gln Lys Arg Leu Met Asp Glu Ala Lys Ile Leu Lys
80 85 90
Ser Leu His His Pro Asn Ile Val Gly Tyr Arg Ala Phe Thr Glu
95 100 105
Ala Asn Asp Gly Ser Leu Cys Leu Ala Met Glu Tyr Gly Gly Glu
110 115 120
Lys Ser Leu Asn Asp Leu Ile Glu Glu Arg Tyr Lys Ala Ser Gln
125 130 135
Asp Pro Phe Pro Ala Ala Ile Ile Leu Lys Val Ala Leu Asn Met
140 145 150
Ala Arg Gly Leu Lys Tyr Leu His Gln Glu Lys Lys Leu Leu His
155 160 165
Gly Asp Ile Lys Ser Ser Asn Val Val Ile Lys Gly Asp Phe Glu
170 175 180
Thr Ile Lys Ile Cys Asp Val Gly Val Ser Leu Pro Leu Asp Glu
185 190 195
Asn Met Thr Val Thr Asp Pro Glu Ala Cys Tyr Ile Gly Thr Glu
200 205 210
Pro Trp Lys Pro Lys Glu Ala Val Glu Glu Asn Gly Val Ile Thr
215 220 225
Asp Lys Ala Asp Ile Phe Ala Phe Gly Leu Thr Leu Trp Glu Met
230 235 240
Met Thr Leu Ser Ile Pro His Ile Asn Leu Ser Asn Asp Asp Asp
245 250 255
Asp Glu Asp Lys Thr Phe Asp Glu Ser Asp Phe Asp Asp Glu Ala
260 265 270
Tyr Tyr Ala Ala Leu Gly Thr Arg Pro Pro Ile Asn Met Glu Glu
275 280 285
Leu Asp Glu Ser Tyr Gln Lys Val Ile Glu Leu Phe Ser Val Cys
290 295 300
Thr Asn Glu Asp Pro Lys Asp Arg Pro Ser Ala Ala His Ile Val
305 310 315
Glu Ala Leu Glu Thr Asp Val
320

<210> 22
<211> 802
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature

<223> Incyte Clone Number: 2764911

<400> 22
Met Glu Glu Glu Gly Gly Ser Ser Gly Gly Ala Ala Gly Thr Ser
1 5 10 15
Ala Asp Gly Gly Asp Gly Gly Glu Gln Leu Leu Thr Val Lys His
20 25 30
Glu Leu Arg Thr Ala Asn Leu Thr Gly His Ala Glu Lys Val Gly
35 40 45
Ile Glu Asn Phe Glu Leu Leu Lys Val Leu Gly Thr Gly Ala Tyr
50 55 60
Gly Lys Val Phe Leu Val Arg Lys Ile Ser Gly His Asp Thr Gly
65 70 75
Lys Leu Tyr Ala Met Lys Val Leu Lys Lys Ala Thr Ile Val Gln
80 85 90
Lys Ala Lys Thr Thr Glu His Thr Arg Thr Glu Arg Gln Val Leu
95 100 105
Glu His Ile Arg Gln Ser Pro Phe Leu Val Thr Leu His Tyr Ala
110 115 120
Phe Gln Thr Glu Thr Lys Leu His Leu Ile Leu Asp Tyr Ile Asn
125 130 135
Gly Gly Glu Leu Phe Thr His Leu Ser Gln Arg Glu Arg Phe Thr
140 145 150
Glu His Glu Val Gln Ile Tyr Val Gly Glu Ile Val Leu Ala Leu
155 160 165
Glu His Leu His Lys Leu Gly Ile Ile Tyr Arg Asp Ile Lys Leu
170 175 180
Glu Asn Ile Leu Leu Asp Ser Asn Gly His Val Val Leu Thr Asp
185 190 195
Phe Gly Leu Ser Lys Glu Phe Val Ala Asp Glu Thr Glu Arg Ala
200 205 210
Tyr Ser Phe Cys Gly Thr Ile Glu Tyr Met Ala Pro Asp Ile Val
215 220 225
Arg Gly Gly Asp Ser Gly His Asp Lys Ala Val Asp Trp Trp Ser
230 235 240
Leu Gly Val Leu Met Tyr Glu Leu Leu Thr Gly Ala Ser Pro Phe
245 250 255
Thr Val Asp Gly Glu Lys Asn Ser Gln Ala Glu Ile Ser Arg Arg
260 265 270
Ile Leu Lys Ser Glu Pro Pro Tyr Pro Gln Glu Met Ser Ala Leu
275 280 285
Ala Lys Asp Leu Ile Gln Arg Leu Leu Met Lys Asp Pro Lys Lys
290 295 300
Arg Leu Gly Cys Gly Pro Arg Asp Ala Asp Glu Ile Lys Glu His
305 310 315
Leu Phe Phe Gln Lys Ile Asn Trp Asp Asp Leu Ala Ala Lys Lys
320 325 330
Val Pro Ala Pro Phe Lys Pro Val Ile Arg Asp Glu Leu Asp Val
335 340 345
Ser Asn Phe Ala Glu Glu Phe Thr Glu Met Asp Pro Thr Tyr Ser
350 355 360
Pro Ala Ala Leu Pro Gln Ser Ser Glu Lys Leu Phe Gln Gly Tyr
365 370 375
Ser Phe Val Ala Pro Ser Ile Leu Phe Lys Arg Asn Ala Ala Val
380 385 390
Ile Asp Pro Leu Gln Phe His Met Gly Val Glu Arg Pro Gly Val

```
                395                 400                 405
Thr Asn Val Ala Arg Ser Ala Met Met Lys Asp Ser Pro Phe Tyr
                410                 415                 420
Gln His Tyr Asp Leu Asp Leu Lys Asp Lys Pro Leu Gly Glu Gly
                425                 430                 435
Ser Phe Ser Ile Cys Arg Lys Cys Val His Lys Lys Ser Asn Gln
                440                 445                 450
Ala Phe Ala Val Lys Ile Ile Ser Lys Arg Met Glu Ala Asn Thr
                455                 460                 465
Gln Lys Glu Ile Thr Ala Leu Glu Leu Cys Glu Gly His Pro Asn
                470                 475                 480
Ile Val Lys Leu His Glu Val Phe His Asp Gln Leu His Thr Phe
                485                 490                 495
Leu Val Met Glu Leu Leu Asn Gly Gly Glu Leu Phe Glu Arg Ile
                500                 505                 510
Lys Lys Lys Lys His Phe Ser Glu Thr Glu Ala Ser Tyr Ile Met
                515                 520                 525
Arg Lys Leu Val Ser Ala Val Ser His Met His Asp Val Gly Val
                530                 535                 540
Val His Arg Asp Leu Lys Pro Glu Asn Leu Leu Phe Thr Asp Glu
                545                 550                 555
Asn Asp Asn Leu Glu Ile Lys Ile Ile Asp Phe Gly Phe Ala Arg
                560                 565                 570
Leu Lys Pro Pro Asp Asn Gln Pro Leu Lys Thr Pro Cys Phe Thr
                575                 580                 585
Leu His Tyr Ala Ala Pro Glu Leu Leu Asn Gln Asn Gly Tyr Asp
                590                 595                 600
Glu Ser Cys Asp Leu Trp Ser Leu Gly Val Ile Leu Tyr Thr Met
                605                 610                 615
Leu Ser Gly Gln Val Pro Phe Gln Ser His Asp Arg Ser Leu Thr
                620                 625                 630
Cys Thr Ser Ala Val Glu Ile Met Lys Lys Ile Lys Lys Gly Asp
                635                 640                 645
Phe Ser Phe Glu Gly Glu Ala Trp Lys Asn Val Ser Gln Glu Ala
                650                 655                 660
Lys Asp Leu Ile Gln Gly Leu Leu Thr Val Asp Pro Asn Lys Arg
                665                 670                 675
Leu Lys Met Ser Gly Leu Arg Tyr Asn Glu Trp Leu Gln Asp Gly
                680                 685                 690
Ser Gln Leu Ser Ser Asn Pro Leu Met Thr Pro Asp Ile Leu Gly
                695                 700                 705
Ser Ser Gly Ala Ala Val His Thr Cys Val Lys Ala Thr Phe His
                710                 715                 720
Ala Phe Asn Lys Tyr Lys Arg Glu Gly Phe Cys Leu Gln Asn Val
                725                 730                 735
Asp Lys Ala Pro Leu Ala Lys Arg Arg Lys Met Lys Lys Thr Ser
                740                 745                 750
Thr Ser Thr Glu Thr Arg Ser Ser Ser Ser Glu Ser Ser His Ser
                755                 760                 765
Ser Ser Ser His Ser His Gly Lys Thr Thr Pro Thr Lys Thr Leu
                770                 775                 780
Gln Pro Ser Asn Pro Ala Asp Ser Asn Asn Pro Glu Thr Leu Phe
                785                 790                 795
Gln Phe Ser Asp Ser Val Ala
                800
```

<210> 23
<211> 641
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 3013946

<400> 23
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Met Ala Thr Thr Val Thr Cys Thr Arg Phe Thr Asp Glu Tyr Gln
  1               5                  10                  15
Leu Tyr Glu Asp Ile Gly Lys Gly Ala Phe Ser Val Val Arg Arg
                 20                  25                  30
Cys Val Lys Leu Cys Thr Gly His Glu Tyr Ala Ala Lys Ile Ile
                 35                  40                  45
Asn Thr Lys Lys Leu Ser Ala Arg Asp His Gln Lys Leu Glu Arg
                 50                  55                  60
Glu Ala Arg Ile Cys Arg Leu Leu Lys His Ser Asn Ile Val Arg
                 65                  70                  75
Leu His Asp Ser Ile Ser Glu Glu Gly Phe His Tyr Leu Val Phe
                 80                  85                  90
Asp Leu Val Thr Gly Gly Glu Leu Phe Glu Asp Ile Val Ala Arg
                 95                 100                 105
Glu Tyr Tyr Ser Glu Ala Asp Ala Ser His Cys Ile Gln Gln Ile
                110                 115                 120
Leu Glu Ala Val Leu His Cys His Gln Met Gly Val Val His Arg
                125                 130                 135
Asp Leu Lys Pro Glu Asn Leu Leu Leu Ala Ser Lys Cys Lys Gly
                140                 145                 150
Ala Ala Val Lys Leu Ala Asp Phe Gly Leu Ala Ile Glu Val Gln
                155                 160                 165
Gly Asp Gln Gln Ala Trp Phe Gly Phe Ala Gly Thr Pro Gly Tyr
                170                 175                 180
Leu Ser Pro Glu Val Leu Arg Lys Glu Ala Tyr Gly Lys Pro Val
                185                 190                 195
Asp Ile Trp Ala Cys Gly Val Ile Leu Tyr Ile Leu Leu Val Gly
                200                 205                 210
Tyr Pro Pro Phe Trp Asp Glu Asp Gln His Lys Leu Tyr Gln Gln
                215                 220                 225
Ile Lys Ala Gly Ala Tyr Asp Phe Pro Ser Pro Glu Trp Asp Thr
                230                 235                 240
Val Thr Pro Glu Ala Lys Asn Leu Ile Asn Gln Met Leu Thr Ile
                245                 250                 255
Asn Pro Ala Lys Arg Ile Thr Ala His Glu Ala Leu Lys His Pro
                260                 265                 270
Trp Val Cys Gln Arg Ser Thr Val Ala Ser Met Met His Arg Gln
                275                 280                 285
Glu Thr Val Glu Cys Leu Lys Lys Phe Asn Ala Arg Arg Lys Leu
                290                 295                 300
Lys Gly Ala Ile Leu Thr Thr Met Leu Ala Thr Arg Asn Phe Ser
                305                 310                 315
Ala Lys Ser Leu Leu Asn Lys Lys Ala Asp Gly Val Lys Pro Gln
                320                 325                 330
Thr Asn Ser Thr Lys Asn Ser Ala Ala Ala Thr Ser Pro Lys Gly
                335                 340                 345
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Thr Leu Pro Pro Ala Ala Leu Glu Pro Gln Thr Thr Val Ile His
                350                 355                 360
Asn Pro Val Asp Gly Ile Lys Glu Ser Ser Asp Ser Ala Asn Thr
                365                 370                 375
Thr Ile Glu Asp Glu Asp Ala Lys Ala Pro Arg Val Pro Asp Ile
                380                 385                 390
Leu Ser Ser Val Arg Arg Gly Ser Gly Ala Pro Glu Ala Glu Gly
                395                 400                 405
Pro Leu Pro Cys Pro Ser Pro Ala Pro Phe Gly Pro Leu Pro Ala
                410                 415                 420
Pro Ser Pro Arg Ile Ser Asp Ile Leu Asn Ser Val Arg Arg Gly
                425                 430                 435
Ser Gly Thr Pro Glu Ala Glu Gly Pro Leu Ser Ala Gly Pro Pro
                440                 445                 450
Pro Cys Leu Ser Pro Ala Leu Leu Gly Pro Leu Ser Ser Pro Ser
                455                 460                 465
Pro Arg Ile Ser Asp Ile Leu Asn Ser Val Arg Arg Gly Ser Gly
                470                 475                 480
Thr Pro Glu Ala Lys Gly Pro Ser Pro Val Gly Pro Pro Pro Cys
                485                 490                 495
Pro Ser Pro Thr Ile Pro Gly Pro Leu Pro Thr Pro Ser Arg Lys
                500                 505                 510
Gln Glu Ile Ile Lys Thr Thr Glu Gln Leu Ile Glu Ala Val Asn
                515                 520                 525
Asn Gly Asp Phe Glu Ala Tyr Ala Lys Ile Cys Asp Pro Gly Leu
                530                 535                 540
Thr Ser Phe Glu Pro Glu Ala Leu Gly Asn Leu Val Glu Gly Met
                545                 550                 555
Asp Phe His Arg Phe Tyr Phe Glu Asn Leu Leu Ala Lys Asn Ser
                560                 565                 570
Lys Pro Ile His Thr Thr Ile Leu Asn Pro His Val His Val Ile
                575                 580                 585
Gly Glu Asp Ala Ala Cys Ile Ala Tyr Ile Arg Leu Thr Gln Tyr
                590                 595                 600
Ile Asp Gly Gln Gly Arg Pro Arg Thr Ser Gln Ser Glu Glu Thr
                605                 610                 615
Arg Val Trp His Arg Arg Asp Gly Lys Trp Gln Asn Val His Phe
                620                 625                 630
His Cys Ser Gly Ala Pro Val Ala Pro Leu Gln
                635                 640

<210> 24
<211> 588
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 067967

<400> 24
Met Gly Gly Thr Ala Arg Gly Pro Gly Arg Lys Asp Ala Gly Pro
  1               5                  10                  15
Pro Gly Ala Gly Leu Pro Pro Gln Gln Arg Arg Leu Gly Asp Gly
                 20                  25                  30
Val Tyr Asp Thr Phe Met Met Ile Asp Glu Thr Lys Cys Pro Pro
```

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                35                  40                  45
Cys Ser Asn Val Leu Cys Asn Pro Ser Glu Pro Pro Ser Pro Arg
                50                  55                  60
Arg Leu Asn Met Thr Thr Glu Gln Phe Thr Gly Asp His Thr Gln
                65                  70                  75
His Phe Leu Asp Gly Gly Glu Met Lys Val Glu Gln Leu Phe Gln
                80                  85                  90
Glu Phe Gly Asn Arg Lys Ser Asn Thr Ile Gln Ser Asp Gly Ile
                95                 100                 105
Ser Asp Ser Glu Lys Cys Ser Pro Thr Val Ser Gln Gly Lys Ser
               110                 115                 120
Ser Asp Cys Leu Asn Thr Val Lys Ser Asn Ser Ser Ser Lys Ala
               125                 130                 135
Pro Lys Val Val Pro Leu Thr Pro Glu Gln Ala Leu Lys Gln Tyr
               140                 145                 150
Lys His His Leu Thr Ala Tyr Glu Lys Leu Glu Ile Ile Asn Tyr
               155                 160                 165
Pro Glu Ile Tyr Phe Val Gly Pro Asn Ala Lys Lys Arg His Gly
               170                 175                 180
Val Ile Gly Gly Pro Asn Asn Gly Gly Tyr Asp Asp Ala Asp Gly
               185                 190                 195
Ala Tyr Ile His Val Pro Arg Asp His Leu Ala Tyr Arg Tyr Glu
               200                 205                 210
Val Leu Lys Ile Ile Gly Lys Gly Ser Phe Gly Gln Val Ala Arg
               215                 220                 225
Val Tyr Asp His Lys Leu Arg Gln Tyr Val Ala Leu Lys Met Val
               230                 235                 240
Arg Asn Glu Lys Arg Phe His Arg Gln Ala Ala Glu Glu Ile Arg
               245                 250                 255
Ile Leu Glu His Leu Lys Lys Gln Asp Lys Thr Gly Ser Met Asn
               260                 265                 270
Val Ile His Met Leu Glu Ser Phe Thr Phe Arg Asn His Val Cys
               275                 280                 285
Met Ala Phe Glu Leu Leu Ser Ile Asp Leu Tyr Glu Leu Ile Lys
               290                 295                 300
Lys Asn Lys Phe Gln Gly Phe Ser Val Gln Leu Val Arg Lys Phe
               305                 310                 315
Ala Gln Ser Ile Leu Gln Ser Leu Asp Ala Leu His Lys Asn Lys
               320                 325                 330
Ile Ile His Cys Asp Leu Lys Pro Glu Asn Ile Leu Leu Lys His
               335                 340                 345
His Gly Arg Ser Ser Thr Lys Val Ile Asp Phe Gly Ser Ser Cys
               350                 355                 360
Phe Glu Tyr Gln Lys Leu Tyr Thr Tyr Ile Gln Ser Arg Phe Tyr
               365                 370                 375
Arg Ala Pro Glu Ile Ile Leu Gly Ser Arg Tyr Ser Thr Pro Ile
               380                 385                 390
Asp Ile Trp Ser Phe Gly Cys Ile Leu Ala Glu Leu Leu Thr Gly
               395                 400                 405
Gln Pro Leu Phe Pro Gly Glu Asp Glu Gly Asp Gln Leu Ala Cys
               410                 415                 420
Met Met Glu Leu Leu Gly Met Pro Pro Pro Lys Leu Leu Glu Gln
               425                 430                 435
Ser Lys Arg Ala Lys Tyr Phe Ile Asn Ser Lys Gly Ile Pro Arg
               440                 445                 450
Tyr Cys Ser Val Thr Thr Gln Ala Asp Gly Arg Val Val Leu Val
```

```
                    455                 460                 465
Gly Gly Arg Ser Arg Arg Gly Lys Lys Arg Gly Pro Pro Gly Ser
                    470                 475                 480
Lys Asp Trp Gly Thr Ala Leu Lys Gly Cys Asp Asp Tyr Leu Phe
                    485                 490                 495
Ile Glu Phe Leu Lys Arg Cys Leu His Trp Asp Pro Ser Ala Arg
                    500                 505                 510
Leu Thr Pro Ala Gln Ala Leu Arg His Pro Trp Ile Ser Lys Ser
                    515                 520                 525
Val Pro Arg Pro Leu Thr Thr Ile Asp Lys Val Ser Gly Lys Arg
                    530                 535                 540
Val Val Asn Pro Ala Ser Ala Phe Gln Gly Leu Gly Ser Lys Leu
                    545                 550                 555
Pro Pro Val Val Gly Ile Ala Asn Lys Leu Lys Ala Asn Leu Met
                    560                 565                 570
Ser Glu Thr Asn Gly Ser Ile Pro Leu Cys Ser Val Leu Pro Lys
                    575                 580                 585
Leu Ile Ser


<210> 25
<211> 389
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 346275

<400> 25
Met Ser Asp Val Cys Ser Ser Gln Arg Ala Glu His Glu His Leu
  1               5                  10                  15
Pro Gly Leu Val Pro Pro Pro Ser Gly Met Gly Val Arg Lys Gly
                 20                  25                  30
Ser Ser Pro Leu Lys Ser His Pro Cys Arg Glu Lys Ser Val Ser
                 35                  40                  45
Asn Arg Arg Ser Gly Lys Thr Ile Val Arg Ser Ala Val Glu Glu
                 50                  55                  60
Val Arg Thr Ala Gly Leu Phe Arg Ser Gly Phe Ser Glu Glu Lys
                 65                  70                  75
Ala Thr Gly Lys Leu Phe Ala Val Lys Cys Ile Pro Lys Lys Ala
                 80                  85                  90
Leu Lys Gly Lys Glu Ser Ser Ile Glu Asn Glu Ile Ala Val Leu
                 95                 100                 105
Arg Lys Ile Lys His Glu Asn Ile Val Ala Leu Glu Asp Ile Tyr
                110                 115                 120
Glu Ser Pro Asn His Leu Tyr Leu Val Met Gln Leu Val Ser Gly
                125                 130                 135
Gly Glu Leu Phe Asp Arg Ile Val Glu Lys Gly Phe Tyr Thr Glu
                140                 145                 150
Lys Asp Ala Ser Thr Leu Ile Arg Gln Val Leu Asp Ala Val Tyr
                155                 160                 165
Tyr Leu His Arg Met Gly Ile Val His Arg Asp Leu Lys Pro Glu
                170                 175                 180
Asn Leu Leu Tyr Tyr Ser Gln Asp Glu Glu Ser Lys Ile Met Ile
                185                 190                 195
```

```
Ser Asp Phe Gly Leu Ser Lys Met Glu Gly Lys Gly Asp Val Met
                200                 205                 210
Ser Thr Ala Cys Gly Thr Pro Gly Tyr Val Ala Pro Glu Val Leu
                215                 220                 225
Ala Gln Lys Pro Tyr Ser Lys Ala Val Asp Cys Trp Ser Ile Gly
                230                 235                 240
Val Ile Ala Tyr Ile Leu Leu Cys Gly Tyr Pro Pro Phe Tyr Asp
                245                 250                 255
Glu Asn Asp Ser Lys Leu Phe Glu Gln Ile Leu Lys Ala Glu Tyr
                260                 265                 270
Glu Phe Asp Ser Pro Tyr Trp Asp Asp Ile Ser Asp Ser Ala Lys
                275                 280                 285
Asp Phe Ile Arg Asn Leu Met Glu Lys Asp Pro Asn Lys Arg Tyr
                290                 295                 300
Thr Cys Glu Gln Ala Ala Arg His Pro Trp Ile Ala Gly Asp Thr
                305                 310                 315
Ala Leu Asn Lys Asn Ile His Glu Ser Val Ser Ala Gln Ile Arg
                320                 325                 330
Lys Asn Phe Ala Lys Ser Lys Trp Arg Gln Ala Phe Asn Ala Thr
                335                 340                 345
Ala Val Val Arg His Met Arg Lys Leu His Leu Gly Ser Ser Leu
                350                 355                 360
Asp Ser Ser Asn Ala Ser Val Ser Ser Ser Leu Ser Leu Ala Ser
                365                 370                 375
Gln Lys Asp Cys Ala Tyr Val Ala Lys Pro Glu Ser Leu Ser
                380                 385
```

<210> 26
<211> 343
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 283746

<400> 26

```
Met Ile Gly Glu Glu Ala Met Ile Asn Tyr Glu Asn Phe Leu Lys
  1               5                  10                  15
Val Gly Glu Lys Ala Gly Ala Lys Cys Lys Gln Phe Phe Thr Ala
                 20                  25                  30
Lys Val Phe Ala Lys Leu Leu His Thr Asp Ser Tyr Gly Arg Ile
                 35                  40                  45
Ser Ile Met Gln Phe Phe Asn Tyr Val Met Arg Lys Val Trp Leu
                 50                  55                  60
His Gln Thr Arg Ile Gly Leu Ser Leu Tyr Asp Val Ala Gly Gln
                 65                  70                  75
Gly Tyr Leu Arg Glu Ser Asp Leu Glu Asn Tyr Ile Leu Glu Leu
                 80                  85                  90
Ile Pro Thr Leu Pro Gln Leu Asp Gly Leu Glu Lys Ser Phe Tyr
                 95                 100                 105
Ser Phe Tyr Val Cys Thr Ala Val Arg Lys Phe Phe Phe Phe Leu
                110                 115                 120
Asp Pro Leu Arg Thr Gly Lys Ile Lys Ile Gln Asp Ile Leu Ala
                125                 130                 135
```

```
Cys Ser Phe Leu Asp Asp Leu Leu Glu Leu Arg Asp Glu Glu Leu
                140                 145                 150
Ser Lys Glu Ser Gln Glu Thr Asn Trp Phe Ser Ala Pro Ser Ala
                155                 160                 165
Leu Arg Val Tyr Gly Gln Tyr Leu Asn Leu Asp Lys Asp His Asn
                170                 175                 180
Gly Met Leu Ser Lys Glu Glu Leu Ser Arg Tyr Gly Thr Ala Thr
                185                 190                 195
Met Thr Asn Val Phe Leu Asp Arg Val Phe Gln Glu Cys Leu Thr
                200                 205                 210
Tyr Asp Gly Glu Met Asp Tyr Lys Thr Tyr Leu Asp Phe Val Leu
                215                 220                 225
Ala Leu Glu Asn Arg Lys Glu Pro Ala Ala Leu Gln Tyr Ile Phe
                230                 235                 240
Lys Leu Leu Asp Ile Glu Asn Lys Gly Tyr Leu Asn Val Phe Ser
                245                 250                 255
Leu Asn Tyr Phe Phe Arg Ala Ile Gln Glu Leu Met Lys Ile His
                260                 265                 270
Gly Gln Asp Pro Val Ser Phe Gln Asp Val Lys Asp Glu Ile Phe
                275                 280                 285
Asp Met Val Lys Pro Lys Asp Pro Leu Lys Ile Ser Leu Gln Asp
                290                 295                 300
Leu Ile Asn Ser Asn Gln Gly Asp Thr Val Thr Thr Ile Leu Ile
                305                 310                 315
Asp Leu Asn Gly Phe Trp Thr Tyr Glu Asn Arg Glu Ala Leu Val
                320                 325                 330
Ala Asn Asp Ser Glu Asn Ser Ala Asp Leu Asp Asp Thr
                335                 340
```

<210> 27
<211> 184
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 2696537

<400> 27

```
Met Gly Asn Gly Met Asn Lys Ile Leu Pro Gly Leu Tyr Ile Gly
  1               5                  10                  15
Asn Phe Lys Asp Ala Arg Asp Ala Glu Gln Leu Ser Lys Asn Lys
                 20                  25                  30
Val Thr His Ile Leu Ser Val His Asp Ser Ala Arg Pro Met Leu
                 35                  40                  45
Glu Gly Val Lys Tyr Leu Cys Ile Pro Ala Ala Asp Ser Pro Ser
                 50                  55                  60
Gln Asn Leu Thr Arg His Phe Lys Glu Ser Ile Lys Phe Ile His
                 65                  70                  75
Glu Cys Arg Leu Arg Gly Glu Ser Cys Leu Val His Cys Leu Ala
                 80                  85                  90
Gly Val Ser Arg Ser Val Thr Leu Val Ile Ala Tyr Ile Met Thr
                 95                 100                 105
Val Thr Asp Phe Gly Trp Glu Asp Ala Leu His Thr Val Arg Ala
                110                 115                 120
```

```
Gly Arg Ser Cys Ala Asn Pro Asn Val Gly Phe Gln Arg Gln Leu
                125                 130                 135
Gln Glu Phe Glu Lys His Glu Val His Gln Tyr Arg Gln Trp Leu
                140                 145                 150
Lys Glu Glu Tyr Gly Glu Ser Pro Leu Gln Asp Ala Glu Glu Ala
                155                 160                 165
Lys Asn Ile Leu Ala Ala Pro Gly Ile Leu Lys Phe Trp Ala Phe
                170                 175                 180
Leu Arg Arg Leu


<210> 29
<211> 118
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 619292

<400> 29
Met Gly Leu Ile Asp Gly Met His Thr His Leu Gly Ala Pro Gly
  1               5                  10                  15
Leu Tyr Ile Gln Thr Leu Leu Pro Gly Ser Pro Ala Ala Ala Asp
                 20                  25                  30
Gly Arg Leu Ser Leu Gly Asp Arg Ile Leu Glu Val Asn Gly Ser
                 35                  40                  45
Ser Leu Leu Gly Leu Gly Tyr Leu Arg Ala Val Asp Leu Ile Arg
                 50                  55                  60
His Gly Gly Lys Lys Met Arg Phe Leu Val Ala Lys Ser Asp Val
                 65                  70                  75
Gly Lys Gln Pro Arg Arg Ser Ile Ser Ala Arg Pro Leu Ser Arg
                 80                  85                  90
Gly Ala Ala Arg Thr Pro Pro Gln Ala Arg His Pro Val Pro Pro
                 95                 100                 105
Gly Asp Thr Gly Leu Pro Pro Ala Phe Val Pro Val Leu
                110                 115


<210> 30
<211> 356
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 2054049

<400> 30
Met Val Gly Val Ser Gly Lys Arg Ser Lys Glu Asp Glu Lys Tyr
  1               5                  10                  15
Leu Gln Ala Ile Met Asp Ser Asn Ala Gln Ser His Lys Ile Phe
                 20                  25                  30
Ile Phe Asp Ala Arg Pro Ser Val Asn Ala Val Ala Asn Lys Ala
                 35                  40                  45
Lys Gly Gly Gly Tyr Glu Ser Glu Asp Ala Tyr Gln Asn Ala Glu
```

50 55 60
Leu Val Phe Leu Asp Ile His Asn Ile His Val Met Arg Glu Ser
65 70 75
Leu Arg Lys Leu Lys Glu Ile Val Tyr Pro Asn Ile Glu Glu Thr
80 85 90
His Trp Leu Ser Asn Leu Glu Ser Thr His Trp Leu Glu His Ile
95 100 105
Lys Leu Ile Leu Ala Gly Ala Leu Arg Ile Ala Asp Lys Val Glu
110 115 120
Ser Gly Lys Thr Ser Val Val Val His Cys Ser Asp Gly Trp Asp
125 130 135
Arg Thr Ala Gln Leu Thr Ser Leu Ala Met Leu Met Leu Asp Gly
140 145 150
Tyr Tyr Arg Thr Ile Arg Gly Phe Glu Val Leu Val Glu Lys Glu
155 160 165
Trp Leu Ser Phe Gly His Arg Phe Gln Leu Arg Val Gly His Gly
170 175 180
Asp Lys Asn His Ala Asp Ala Asp Arg Ser Pro Val Phe Leu Gln
185 190 195
Phe Ile Asp Cys Val Trp Gln Met Thr Arg Gln Phe Pro Thr Ala
200 205 210
Phe Glu Phe Asn Glu Tyr Phe Leu Ile Thr Ile Leu Asp His Leu
215 220 225
Tyr Ser Cys Leu Phe Gly Thr Phe Leu Cys Asn Ser Glu Gln Gln
230 235 240
Arg Gly Lys Glu Asn Leu Pro Lys Arg Thr Val Ser Leu Trp Ser
245 250 255
Tyr Ile Asn Ser Gln Leu Glu Asp Phe Thr Asn Pro Leu Tyr Gly
260 265 270
Ser Tyr Ser Asn His Val Leu Tyr Pro Val Ala Ser Met Arg His
275 280 285
Leu Glu Leu Trp Val Gly Tyr Tyr Ile Arg Trp Asn Pro Arg Met
290 295 300
Lys Pro Gln Glu Pro Ile His Asn Arg Tyr Lys Glu Leu Leu Ala
305 310 315
Lys Arg Ala Glu Leu Gln Lys Lys Val Glu Glu Leu Gln Arg Glu
320 325 330
Ile Ser Asn Arg Ser Thr Ser Ser Ser Glu Arg Ala Ser Ser Pro
335 340 345
Ala Gln Cys Val Thr Pro Val Gln Thr Val Val
350 355

<210> 31
<211> 453
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 2843910

<400> 31
Met Ala Gly Ala Gly Gly Phe Gly Cys Pro Ala Gly Gly Asn Asp
1 5 10 15
Phe Gln Trp Cys Phe Ser Gln Val Lys Gly Ala Ile Asp Glu Asp

```
                20                      25                      30
Val Ala Glu Ala Asp Ile Ile Ser Thr Val Glu Phe Asn Tyr Ser
                35                      40                      45
Gly Asp Leu Leu Ala Thr Gly Asp Lys Gly Gly Arg Val Val Ile
                50                      55                      60
Phe Gln Arg Glu Gln Glu Asn Lys Ser Arg Pro His Ser Arg Gly
                65                      70                      75
Glu Tyr Asn Val Tyr Ser Thr Phe Gln Ser His Glu Pro Glu Phe
                80                      85                      90
Asp Tyr Leu Lys Ser Leu Glu Ile Glu Glu Lys Ile Asn Lys Ile
                95                      100                     105
Arg Trp Leu Pro Gln Gln Asn Ala Ala His Phe Leu Leu Ser Thr
                110                     115                     120
Asn Asp Lys Thr Ile Lys Leu Trp Lys Ile Ser Glu Arg Asp Lys
                125                     130                     135
Arg Ala Glu Gly Tyr Asn Leu Lys Asp Glu Asp Gly Arg Leu Arg
                140                     145                     150
Asp Pro Phe Arg Ile Thr Ala Leu Arg Val Pro Ile Leu Lys Pro
                155                     160                     165
Met Asp Leu Met Val Glu Ala Ser Pro Arg Arg Ile Phe Ala Asn
                170                     175                     180
Ala His Thr Tyr His Ile Asn Ser Ile Ser Val Asn Ser Asp His
                185                     190                     195
Glu Thr Tyr Leu Ser Ala Asp Asp Leu Arg Ile Asn Leu Trp His
                200                     205                     210
Leu Glu Ile Thr Asp Arg Ser Phe Asn Ile Val Asp Ile Lys Pro
                215                     220                     225
Ala Asn Met Glu Glu Leu Thr Glu Val Ile Thr Ala Ala Glu Phe
                230                     235                     240
His Pro His Gln Cys Asn Val Phe Val Tyr Ser Ser Ser Lys Gly
                245                     250                     255
Thr Ile Arg Leu Cys Asp Met Arg Ser Ser Ala Leu Cys Asp Arg
                260                     265                     270
His Ser Lys Phe Phe Glu Glu Pro Glu Asp Pro Ser Ser Arg Ser
                275                     280                     285
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His Ser Gly Arg Tyr Met Met Thr Arg Asp Tyr Leu Ser Val Lys
                305                     310                     315
Val Trp Asp Leu Asn Met Glu Ser Arg Pro Val Glu Thr His Gln
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Val His Glu Tyr Leu Arg Ser Lys Leu Cys Ser Leu Tyr Glu Asn
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Ser Ala Ile Met Thr Gly Ser Tyr Asn Asn Phe Phe Arg Met Phe
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Asp Arg Asp Thr Arg Arg Asp Val Thr Leu Glu Ala Ser Arg Glu
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Ser Ser Lys Pro Arg Ala Ser Leu Lys Pro Arg Lys Val Cys Thr
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Gly Gly Lys Arg Arg Lys Asp Glu Ile Ser Val Asp Ser Leu Asp
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Phe Asn Lys Lys Ile Leu His Thr Ala Trp His Pro Val Asp Asn
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<211> 1260
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<213> Homo sapiens

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<211> 2059
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte Clone Number: 940589

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<213> Homo sapiens

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<223> Incyte Clone Number: 304421

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<211> 4416
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<213> Homo sapiens

<220>
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<212> DNA
<213> Homo sapiens

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<223> Incyte Clone Number: 1378134

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<223> Incyte Clone Number: 3013946

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<211> 2140
<212> DNA

<213> Homo sapiens

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<223> Incyte Clone Number: 067967

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<212> DNA
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<223> Incyte Clone Number: 346275

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<213> Homo sapiens

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